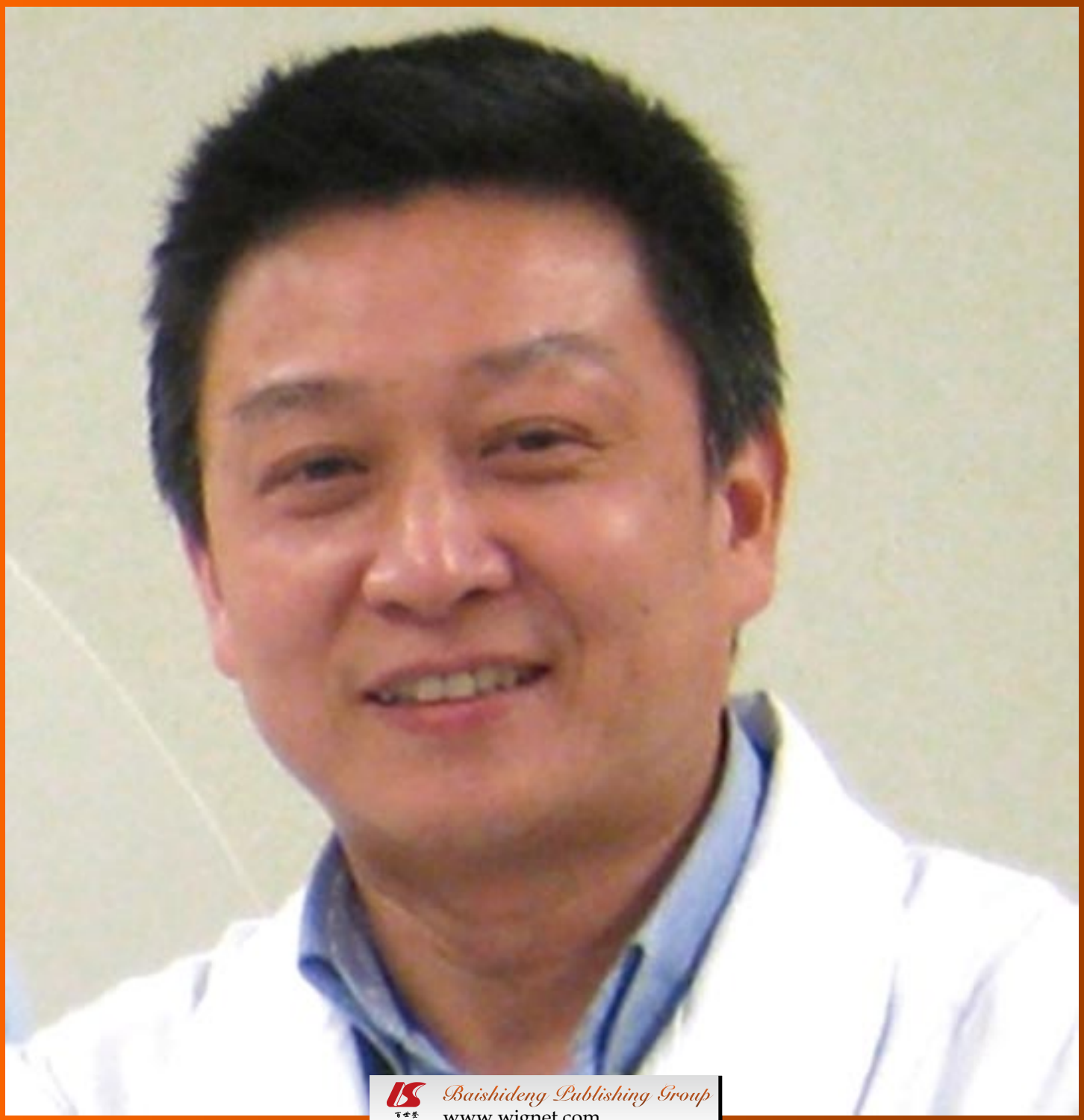
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REVIEW

Dissolution mechanism of calcium apatites in acids: A review of literature

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Abstract

Eight dissolution models of calcium apatites (both fluorapatite and hydroxyapatite) in acids were drawn from the published literature, analyzed and discussed. Major limitations and drawbacks of the models were conversed in details. The models were shown to deal with different aspects of apatite dissolution phenomenon and none of them was able to describe the dissolution process in general. Therefore, an attempt to combine the findings obtained by different researchers was performed which resulted in creation of the general description of apatite dissolution in acids. For this purpose, eight dissolution models were assumed to complement each other and provide the correct description of the specific aspects of apatite dissolution. The general description considers all possible dissolution stages involved and points out to some missing and unclear phenomena to be experimentally studied and verified in future. This creates a new methodological approach to investigate reaction mechanisms based on sets of affine data, obtained by various research groups under dissimilar experimental conditions.

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Key words: Calcium orthophosphates; Fluorapatite; Hydroxyapatite; Dissolution; Model; Mechanism

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INTRODUCTION

Calcium apatites [hydroxyapatite (HA): $Ca_{10}(PO_4)_6(OH)_2$ and fluorapatite (FA): $Ca_{10}(PO_4)_6F_2$] appear to be of a special interest to the mankind, because natural apatites are the main source of inorganic phosphorus in nature[1], while calcified tissues (bones and teeth) of mammals consist of ion-substituted calcium apatites of biological origin[2-4]. Therefore, HA and FA are widely used in various aspects of human being, starting from the major source of phosphorus-containing fertilizer production and ending with various biomedical applications, for example, using as artificial bone grafts. The latter resulted in a great number of research papers published on calcium apatites and related calcium orthophosphates[5-7]. Since the chemical nature of natural phosphate ores and the inorganic phase of bones and teeth is almost the same, such different processes as fertilizer production, dental caries, osteoporosis, as well as both *in vitro* and *in vivo* biodegradation of artificial bone grafts might be simulated by dissolution of chemically pure calcium apatites (HA and FA) in acids. Therefore, establishing of the true dissolution mechanism of calcium apatites in acids appears to be of the paramount importance for our species.

In chemistry, a reaction mechanism is the step by step sequence of elementary reactions by which the overall chemical change occurs[8]. Regarding the dissolution process of calcium apatites in acids, eight models have been already proposed to explain the processes

involved. These models already provided the important information about the factors associated with solution (pH, composition, saturation and hydrodynamics), bulk solid (chemical composition, solubility, particle sizes) and surface (defects, adsorbed ions, "history", phase transformation) of the apatite crystals. These findings cannot be underestimated because they have already made a significant impact on understanding of the medical aspects of both dental caries and osteoporosis, as well as they created the necessary fundamentals for fertilizer production industry. Nevertheless, there are still a lot of elements missing in the overall explanation for the processes involved.

To clarify possible directions of further investigations on apatite dissolution, a critical analysis of currently available models has been made in this review followed by an attempt to combine the data available into a general dissolution mechanism. This creates a new methodological approach to investigate reaction mechanisms based on sets of affine data, obtained by various research groups under dissimilar experimental conditions.

CRITICAL ANALYSIS OF THE DISSOLUTION MODELS OF CALCIUM APATITES

Diffusion (or transport) and kinetically (or surface) controlled models

A diffusion (or transport) and a kinetically (or surface) controlled[9-30] dissolution models, as well as the two-site model[15,31-33], are devoted to comparison of transport rates of chemical reagents (H^+ and anions of acid) from bulk solution to the surface of apatite crystals and those of products (Ca^{2+}, F^- and orthophosphate anions) obtained backwards with the kinetics of chemical interactions on the crystal surface. According to the diffusion-controlled and two-site models, a transport of either the chemical reagents and/or the products of chemical reactions mainly determine the overall dissolution rate, whereas the kinetically controlled model emphasizes chemical transformations on the surface as the limiting factor (Figure 1)[34]. An important consequence of the two types of rate-controlling mechanism is that the solution immediately next to the crystal surface is undersaturated with respect to apatite in the surface controlled process and this solution is saturated in the diffusion-controlled process[35]. Both models usually operate with a so-called "driving force" which means either a concentration gradient within the Nernst diffusion layer (the diffusion controlled model) or a gradient of ionic chemical potentials between the apatite crystal surface and bulk solution (the kinetically controlled model).

To investigate whether a dissolution process follows either of these models, one should study the influence of hydrodynamics, concentration of reagents, ionic strength, solution undersaturation, pH, temperature, crystal dimensions and the presence of chemical modifiers on the dissolution kinetics. A rotary disk[10,13,14], constant composition[9,16,18,19,20,36-38] or dual constant composition[22,38,39] techniques are used for experimental investigations. The results obtained are usually plotted as an uptake of H^+ ions (e.g., as a titrant volume added) and/or a release of calcium, orthophosphate and fluoride ions versus the dissolution time. Afterwards, calculations of the numeric values for activation energy, rate constants, effective reaction order, diffusion layer thickness, characteristic adsorption impedance, diffusive jump distance, *etc.*, are performed[9-33,36-40]. The conclusion on whether a dissolution process is kinetically or diffusion controlled is made based on the numeric values calculated. For example, when analysis of the rate data gave a numeric value of the effective reaction order $n = 6$, a surface controlled dissolution mechanism was suggested[22].

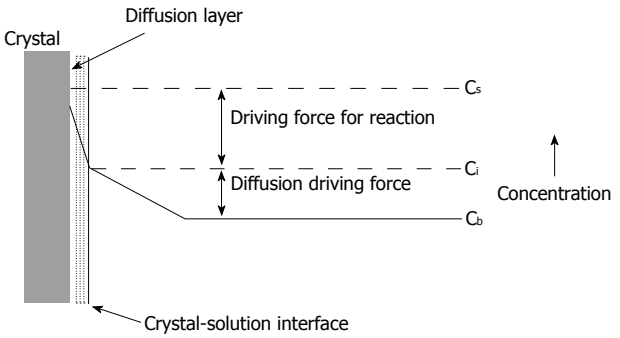


Figure 1 A dissolution process according to the diffusion and kinetically controlled models. C_s: Solute concentration on the surface; C_i: Solute concentration on the interface; C_b: Solute concentration in bulk. Reprinted from Ref.[34] with permission.

Basic thermodynamic principles predict that dissolution rates should increase with increasing driving force or chemical potential; however, the experimental studies show that this dependence is complex. Namely, dissolution of apatite in some cases was found to be diffusion controlled[19,20,23,25], in some other cases - kinetically controlled[21,22] and even intermediate (i.e., both kinetically and diffusion controlled) in still other cases[14]. Furthermore, the dissolution process might be composed of two stages: the first one was found to be both surface and diffusion controlled, while the second one was an exactly diffusion-controlled dissolution[24]. Therefore, the results obtained for these models are valid within the experimental conditions studied only; no extrapolation can be made outside the ranges studied. For example, after, say, an agitation decreasing or temperature increasing, an initially kinetically controlled dissolution might be controlled by diffusion[30].

Furthermore, in some cases, dissolution curves (a titrant volume against time) reach plateaus prior to complete dissolution of HA, thus indicating a creation of metastable states in which the reaction is effectively terminated even though apatite crystals remain in contact with the undersaturated solutions[41-53]. There is an opinion[54] that this effect resulted from a false solubility product value for HA. Thus, a high sensitivity to the experimental conditions appears to be the main drawback of these models.

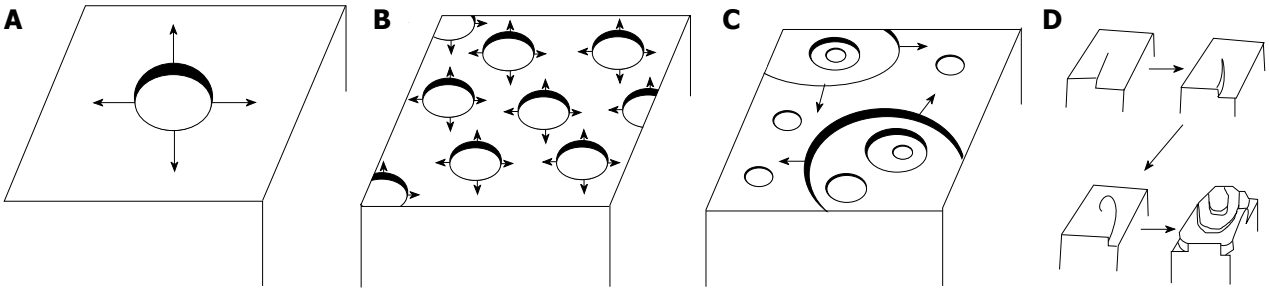


Figure 2 A dissolution process according to the mono- and polynuclear models. A: Mononuclear model; B: Polynuclear model in one crystal step; C: Polynuclear model in multiple steps: birth and spread; D: Spiral model. Reprinted from Ref.[34] with permission.

Mono- and polynuclear models

The surface dissolution may be described by three different models shown schematically in Figure 2. As may be seen in Figure 2A it is possible to start dissolution from one center from which originates the units detachment leading to step disintegration. This is a mononuclear dissolution. It is also possible that detachment takes place simultaneously from multiple centers (Figure 2B and C) which may be developed in one or more steps on the crystal surface. This is a polynuclear dissolution. Alternatively, it has been suggested that the crystal units' detachment takes place along spirals originating from an active site on the crystal surface following an Archimedean spiral (Figure 2D). The unit detachment along the spirals takes place at constant velocity[34].

A polynuclear model[55-64] was created from the study on apatite dissolution and growth kinetics under the constant composition conditions. Polydispersed samples of apatite were put into a stirred undersaturated (for dissolution experiments) or supersaturated (for those on crystal growth) solutions and the solution pH and amount of chemicals added (an acid for the dissolution experiments and a base for those on crystal growth) were permanently recorded as functions of time. The results obtained were plotted versus either undersaturation or supersaturation values: straight lines were obtained in the specific logarithmic coordinates typical for this model[65]. According to this model, dissolution nuclei, i.e., collections of vacant sites for Ca^{2+}, PO_4^{3-} and OH^- ions, are formed on the crystal surface of apatite and spread over the surface with a definite lateral rate[56].

In polynuclear model, the nucleation rate is assumed as a function of the mean ion activity. A lateral growth rate of the nuclei is assumed proportional to the difference between the total concentration of calcium ions in the saturated solution and in a solution, while the rate constant is related to the frequency for calcium ions to make a diffusion jump into a kink and, simultaneously, partly dehydrate[62,63]. Investigations on apatite dissolution and crystal growth using atomic force microscopy revealed that the rate-determining step was not the diffusion but two-dimensional surface nucleation[66,67]. These observations provided a valuable support for the polynuclear model.

The experimental data on dissolution and growth rates versus undersaturation ($S < 1$) and supersaturation ($S > 1$) values, respectively, were obtained. Numeric values of surface tension (40 mJ/m^2 for apatite dissolution and 100 mJ/m^2 for apatite growth[62,63]), ionic frequencies to enter or leave a kink ($1.6 \times 10^5/s$[61]), the mean distance between kinks in a surface nucleus (approximately 3.07 Å[60]) and the critical nuclei for both HA[55-59,62,63] and FA[60,61] were calculated. Furthermore, within $5.0 < pH < 7.2$ the dissolution kinetics was found to follow the polynuclear model, while that of growth appeared to follow the polynuclear model within $5.5 < pH < 6.5$ and the combined mono-polynuclear model at $pH = 5.0$[60,61].

A new idea about hydroxide ions formation at the hydroxide sites of HA from water molecules trapped under the crystal surface appeared in the most recent papers of this series[62,63]. Probably, this might be a reason for the above changing in the growth model found for HA at $pH = 5.0$. To conclude, the polynuclear model seems to be better elaborated among others because it is valid for apatite dissolution within solution pH of 5.0-7.2, saturation degrees of $0.1 < S < 7$, and Ca/P molar ratios of 0.1-20[63]. However, nothing has been published on a validity of this model in more acidic solutions.

Self-inhibition (calcium-rich layer formation) model

A model with a self-inhibition layer formation describes a formation of a calcium-rich layer on the surface of apatite during dissolution[19,49-53]. This model was created from the results on dissolution kinetics of apatite powders in acidic buffers at solution pH within 3.7-6.9 (the constant composition technique was used). Following concentration of calcium and solution pH, the authors found that during the initial period (2-5 min) of dissolution release of calcium into the bulk solution was always less when compared with consumption of H^+. When dissolution progressed, rates of calcium release permanently increased and hydrogen uptake decreased until the equivalence (consumption of two hydrogen resulted in release of one calcium) was reached, while the over-all rate of apatite dissolution permanently decreased[19,49-53]. Similar decreasing of apatite dissolution rates were obtained by other research groups[41-48,68].

According to this model, apatite is dissolved by ionic detachment of calcium and orthophosphate ions from the surface to a solution. When an initial portion of apa-

tite has been dissolved, some amount of calcium cations (presumably, in connection with anionic counter ions) is returned from the solution and adsorbed back onto the surface of apatite. The latter results in formation of a semi-permeable ionic membrane consisting of a positively charged layer containing strongly adsorbed calcium ions, i.e., a calcium-rich layer is formed[19,49-53]. An indirect confirmation of the presence of a calcium-rich layer was obtained in the most recent paper of this series: for initial strong calcium undersaturation in solutions, attainment of a pseudo-steady state was very long[53]. The areas per adsorbed single PO_4^{3-} and Ca^{2+} ions on HA surface at the point of zero charge (pH = 8.5) were estimated to be 33.1 ± 2.7 and 23.0 ± 2.1 $Å^2$, respectively[69].

The authors of calcium-rich layer formation model suggested that the rate control of apatite dissolution was diffusion of calcium and/or orthophosphate ions through an interfacial surface layer formed during the initial portion of the dissolution process. This interface would be composed of the Nernst layer that would be adjacent to the calcium-rich layer. This last one would present low permeability making the dissolution process slower[19,49-53]. It is important to notice that these conclusions were made from the experiments on following calcium concentration and solution pH only; no measurements of the surface composition of apatites were performed.

As said by this model, ionic diffusion in solution results in a situation when ionic concentration near the surface layer of apatite is always higher than that in the bulk solution. Calcium concentration in the solution is also inhomogeneous: it decreases when the distance from the liquid/solid interfaces increases[19,49-53]. Therefore, the calcium-rich layer appears to be undoubtedly rich in calcium when compared with the bulk solution only. However, when compared with the bulk of solid apatite (Ca/P = 1.67) this layer appears to be calcium-rich (Ca/P > 1.67) when the counter anions A^{n-} (it is assumed, that apatite is dissolved in acid H_nA, where A^{n-} is an anion) adsorbed from the solution are not taken into account. If the counter anions are calculated, a numeric value for Ca/(P+A) molar ratio on the surface will be around 1.67 in the case of zero charge on the surface.

On the other hand, ions of calcium might be adsorbed without the counter anions. This results in an electrical double layer formation on the solid/liquid interface with positive charge on apatite. Indeed, apatite is charged positively in acidic solutions. This effect was explained by adsorption of either protons only[70] or protons and calcium cations from the solution[71,72]. Certainly, the presence of a positive charge on apatite surface is in favor for the calcium-rich layer model but one should not forget that this charge might be caused by adsorption of protons only[70]. The dissolution rate reduction found by the authors and explained by the state of the interface (adsorption of calcium[53]) might also be explained by adsorption of some impurities those always present in the solution. Other explanations are also available[41-48]. Thus, unless the direct measurements of the calcium content on the surface are made, this model cannot be considered as experimentally proven.

A contradiction between the calcium-rich layer formation and polynuclear models can be outlined: sorption of calcium is likely to happen on the dissolution nuclei. In this case, some amount of the nuclei should disappear, as a result. No suggestions how to overcome this contradiction were found in the references.

To conclude this model, one should notice that due to the formation of a calcium-rich layer, a non-stoichiometric (incongruent) dissolution (see the next model) is suggested by default.

Stoichiometric/non-stoichiometric (congruent/incongruent) dissolution

A congruent/incongruent (or stoichiometric/non-stoichiometric) dissolution[11,17,19,21,40,50,68,73-90] is based on the direct measurements of either the ionic concentrations in a solution[19,21,40,68,74-76,80,83,84,87,88,90] or the surface composition of apatites during dissolution[17,77,81]. According to the definitions, ions of a solid might be dissolved either simultaneously with the dissolution rates proportional to their molar concentrations (a congruent dissolution) or non-simultaneously with different values of the dissolution rates for each ion (an incongruent dissolution). The latter case always results in a situation when a surface layer with a chemical composition different from that of the bulk of solid is formed.

For acidic dissolution of FA, ions of F^- were found to dissolve faster (or in a greater ionic proportion) when compared to ions of calcium and orthophosphate[17,68,77,83,88,89]. A similar phenomenon of faster (or in a greater ionic proportion) dissolution of calcium when compared to that of orthophosphate was also found[40,75,76,79-82,90]. In the latter case, a surface layer of acidic calcium orthophosphates, presence of HPO_4^{2-} ions and/or Ca-depleting of the surface were either suggested[52,61,85] or found[81,86,88,89]. Thus, if incongruent dissolution occurs from a stoichiometric HA surface, the surface Ca/P ratio will become lower than for the bulk and a Ca-deficient HA (CDHA) must then be present, even if there is no phase change[54]. However, there are contradictory results. For example, when FA was dissolved, the solution concentrations of calcium and fluoride ions were non-stoichiometrically lower with respect to that of orthophosphate ions due to a possibility that some amount of sparingly soluble calcium fluoride was precipitated[40,86,88-94]. Furthermore, one should mention on a study, in which release of calcium into the bulk solution was always less, when compared with release of orthophosphate[68]. On the other hand, having followed the release kinetics of calcium and orthophosphate ions into solution, apatites were found to dissolve stoichiometricaly (congruently)[21,73,95].

Interestingly, but apatites might be dissolved stoichiometrically or non-stoichiometrically depending on the experimental conditions. For example, CDHA was found to dissolve congruently at the solution pH < 4.5,

while an incongruent dissolution with Ca/P ratio in solution attaining values as high as about 25 was detected in solutions within 4.5 < pH < 8.2. Furthermore, almost negligible dissolution with another type of a non-stoichiometry with Ca/P ratio close to zero in solutions was found at solution pH > 8.2[87]. For 4.5 < pH < 8.2 conditions, the authors explained the incongruent dissolution by re-adsorption of already dissolved orthophosphate anions from the solution onto the positively charged CDHA surface. While in more basic solutions, the surface of CDHA was charged negatively and, thus, the authors suggested a possibility of both re-adsorption of already dissolved calcium cations onto CDHA surface and desorption of orthophosphate ions from the CDHA surface. However, it has to be realized that at solution pH > 8.2 the uncertainties in the chemical analysis of Ca (in particular) and P were relatively high, making any quantitative interpretation of this re-adsorption/desorption difficult[87]. The same effect was discovered in another study[89]. Furthermore, dissolution of both FA and natural sedimentary carbonated FA was found to be incongruent in the early stages but tended toward congruency as the dissolution reaction proceeded to steady state[40,68,96]. According to the authors, this initial incongruency was likely a result of the exchange of solution H^+ ion for mineral bound Ca[40]. Besides, a presence of simple inorganic salts (Na_2SO_4, CH_3COONa or NaCl) in solution appeared to have an influence on the equilibrium concentrations of orthophosphate and calcium ions released from apatite: the order of salts increasing orthophosphate in solution was Na_2SO_4 > CH_3COONa > NaCl, while that increasing calcium was opposite[84]. This effect was explained by a specific affinity of some ions (e.g., sulfate) for apatite and might be a reason for transition of congruent to incongruent dissolution in some cases[92-94,97]. Similarly, presence of other compounds might influence the dissolution congruence[98]. Other reasonable explanations might be due to either experimental difficulties in precise following of Ca/P ratio both in the solution and on the crystal surface or differences in chemical and structural compositions of apatites studied by different researchers (both FA and HA are known to be often non-stoichiometric and calcium-deficient, especially on the surface[2-4,87-89,99]).

The idea on a great influence of a surface layer is supported by the data on dissolution of stoichiometric HA (Ca/P = 1.67) in aqueous solutions within pH 4.90-9.94[76]. The authors found that after removal of an irreversible surface, which generated excessive calcium and orthophosphate solution concentrations, further behavior of HA became reproducible. A surface of one atom-layer thickness or less was believed to have formed during the preparation of the solid[76]. On the other hand, dissolution of HA in aqueous medium appeared to be always non-stoichiometric at the beginning, but when the solid was successively equilibrated at any given pH, the solution Ca/P ratio approached a limiting value of 1.67. Once this value was reached, the solid only maintained this solution ratio by dissolving stoichiometricaly[76]. The authors explained these phenomena by a previous history of the samples studied. A similar conclusion was also made in another paper[74]. Thus, the experimental techniques of apatite preparation might have a great influence to stoichiometry/non-stoichiometry of dissolution. This is a serious drawback.

Finally, the results on theoretical analysis of surface layer formation on HA should be reported[85]. The main point of that paper is an idea that both the stoichiometric HA (Ca/P = 1.67) and any non-stoichiometric CDHA (Ca/P ratio within 1.5-1.67) might be described as the same substance. More precisely, there is a continuous amount of intermediate compounds within $1.5 \leqslant Ca/P \leqslant 1.67$ having the same crystal structure which is drawn as a line on the solubility diagram CaO - P_2O_5 - H_2O[85]. Furthermore, according to the authors, at the steady state, both HA and CDHA are dissolved congruently only when both the solution and solid have the same Ca/P ratio. Therefore, any sample of HA and CDHA is dissolved incongruently except the only one solution composition having the similar Ca/P ratio with that particular sample. In all other cases, a surface layer having a Ca/P ratio less than 1.67, which is often used as the indication of incongruent dissolution of apatite, will form as a result (this, however, depends on the accuracy with which the analyses can be made)[85]. Thus, whether apatites are dissolved congruently or incongruently might also depend on both their initial chemical composition and the solution properties.

To conclude, one should notice that all the aforementioned cases of incongruent dissolution of both FA and HA describe the formation of a surface layer of a CDHA and/or acidic calcium orthophosphates, which is calcium-depleted when compared to the bulk apatite. Thus, there is a disagreement between the incongruent dissolution and calcium-rich layer formation model. Perhaps, this might be due to the differences in experimental conditions.

Chemical model

A chemical dissolution model was proposed as well[100-102]. This model was developed from a self-evident supposition that it would be highly unlikely if apatite were dissolved by detachment of "single molecules" equal to the unit cells and consisting of 18 ions. Moreover, in the crystal lattice all ions are shared with neighboring unit cells and often cannot be attributed to the given "single molecule". Therefore, based on the experimental results obtained on the one hand and an analysis of the data found in references on the other hand, a sequence of four successive chemical reactions:

$$Ca_5(PO_4)_3(F,OH) + H_2O + H^+ = Ca_5(PO_4)_3(H_2O)^+ + HF,H_2O \quad (1)$$

$$2Ca_5(PO_4)_3(H_2O)^+ = 3Ca_3(PO_4)_2 + Ca^{2+} + 2H_2O \quad (2)$$

$$Ca_3(PO_4)_2 + 2H^+ = Ca^{2+} + 2CaHPO_4 \quad (3)$$

$$CaHPO_4 + H^+ = Ca^{2+} + H_2PO_4^- \quad (4)$$

was proposed to describe the chemical processes of apatite dissolution[100-102]. According to this model, equations

(1)-(4) should be used instead of the well-known net-reactions (5) and (6):

$Ca_5(PO_4)_3(F, OH) + 7H^+ = 5Ca^{2+} + 3H_2PO_4^- + HF, H_2O$ (5)

$Ca_5(PO_4)_3(F, OH) \rightarrow 5Ca^{2+} + 3PO_4^{3-} + F^-, OH^-$ (6)

Chemical model (1)-(4) was initially created for description of apatite dissolution in strong acidic media[101] and appeared to be a further development of some ideas proposed earlier. For example, already in 1960s reactions (5) and (6) had been suggested "not to give the mechanism but merely express net-reactions only"[103]. Later, Pearce[104] and Chow[35] discussed which of net-reactions (5) or (6) described the dissolution process better. For acidic dissolution of apatites, net-reaction (5) represents the direct chemical interaction between the surface of solid apatite and an acidic solution. However, Pearce suggested that, in principle, the dissolution process might also happen according to net-reaction (6) followed by a chemical interaction in the solution among the ions of apatite and acid *near* the crystal surface[104]:

$5Ca^{2+} + 3PO_4^{3-} + F, OH + 7H^+ = 5Ca^{2+} + 3H_2PO_4^- + HF, H_2O$ (7)

In spite of a lack of the experimental techniques, able to follow the detachment of single ions, a reasonable ionic description of apatite dissolution as a system of chemical equations (1)-(4) was created from the indirect measurements[100-102]. According to this model, chemical dissolution of apatite occurs step by step on the surface *via* intermediate formation of a monoatomic layer of some virtual compounds, like $Ca_3(PO_4)_2$ and $CaHPO_4$[100-102]. Both latter substances are known as precursors of apatite formation during chemical crystallization[3,105]. Moreover, based on the sequence of ionic detachment (first fluorine for FA or hydroxide for HA, followed by calcium and afterwards by orthophosphate) it is suggested that dissolution of apatites is always incongruent (non-stoichiometric) at the atomic (ionic) level. However, a lack of the precise experimental verification transforms the chemical model into a reasonable hypothesis only.

To conclude this model, one may assume that some new relations between the kinetically controlled and chemical models might be established in future. Before the chemical model was created, chemistry of apatite dissolution had been always described by equations (5) or (6) + (7). For this reason, the kinetically controlled model was also adapted for these equations. For example, the overall rate constants for net-reactions (5), (6) and (7) are still used for calculations, whereas they are probably equal to either the lowest of the rate constants of (1)-(4) (the rate determining step) or some combination.

Etch pit formation

A process of etch pit formation describes acidic dissolution of apatite crystals containing structural defects (dislocations and inclusions)[41-48,96,106-115]. A radius of dislocations outlets (hollow cores) on apatite was calculated to be within 8.3-20 Å for screw dislocations and 18-43 Å for edge ones[109]. The presence of dislocations accelerates dissolution, because dislocations give rise to continuous steps on the surface (Figure 2D) and the strain energy they cause in crystals favors etch pit formation. Thus, the dissolution process of solids is induced by formation of pits (Figure 3) and continues with spreading of their stepwaves[116,117]. As a result, the surface of apatite becomes rough and the total edge length and edge free energy increases[41-48]. These pits provide dissolution sites and the entire reaction proceeds *via* nucleation and growth of the pits accompanying step flow. The pits appear at the dislocation outlets, usually they are 0.1-10 μm in size (their dimensions depend on dissolution kinetics and dissolution time: they increase when the dissolution progresses; furthermore, the crystals must be sufficiently big to provide enough room for large pits to form). The walls and bottom of etch pits consist of crystal faces possessing the highest dissolution rates, which allow them to grow. However, the growth kinetics of etch pits (therefore, the dissolution process of apatites in general) might be suppressed by addition of very simple chemicals, such as NaCl. This phenomenon might be attributed to a competition for surface protonation sites between Na^+ and H^+ ions.

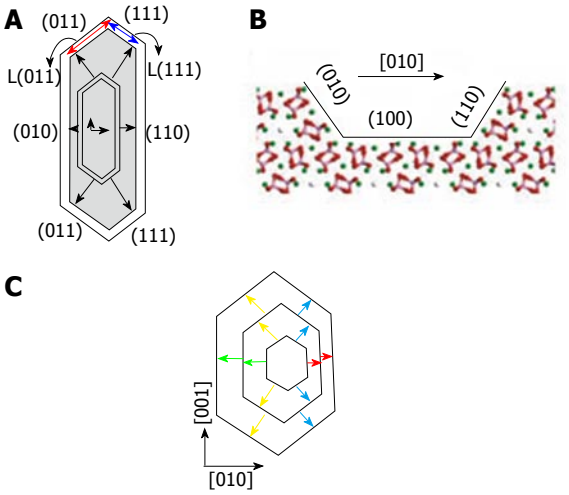


Figure 3 A typical etch pit on the surface of calcium apatites. A: Top view and a model of its evolution during dissolution. Arrows represent relative step velocities displaying different facets; B: View through the [001] direction in the (100) surface. The exposed step faces can be seen to be un-equivalent owing to the opposite orientations of the orthophosphate groups. Reprinted from Ref. [118] with permission; C: Schematic of the evolution of hexagonal etch pits. Four differently colored arrows represent relative step velocities. Reprinted from Ref. [120] with permission.

For dissolution of apatites, the pits usually have a hexagonal shape (Figure 3) according to the crystal symmetry $P6_3/m$ of pure HA and FA[106-111,118-123]. However, their shape might be different (e.g., triangular) when specific ions (e.g., fluoride) are present in a solution[121]. It is important to mention that the growing process of etch pits might be inhomogeneous: movement of the dissolution steps on one side of any single pit might be faster or slower their counterparts on the other side, suggesting the formation of asymmetric pits, as schematically shown in Figures 3A and D. Concerning height of the steps, it appears to depend on both crystal faces and dissolution

conditions. For example, for an HA (100) surface exposed to deionized water, the average height of each step was found to be 0.84 ± 0.1 nm, which is close to the interlayer distance of the (100) surface [d(100) ≈ 0.82 nm]. Furthermore, it remained constant during dissolution[120].

The formation of etch pits on the crystal faces is the driving force for dissolution. However, in the case of nearly physiological conditions and sufficiently low solution undersaturation, a free energy barrier becomes too high for vacancy nucleation to occur on a time scale that is competitive with other processes. Thus, the dissolution process of apatites becomes spontaneous only when etch pits of critical sizes (determined by the Gibbs-Thomson effect, a well-known thermodynamic principle) are reached[41-48]. At this critical size, the free energy change goes through a maximum that defines an energy barrier to a pit formation. Therefore, only relatively large pits (of sizes greater than a critical value) appear to be active, with stepwaves contributing to dissolution, while the spreading velocities are also dependent on the pit sizes, decreasing with pit size decreasing. Moreover, during dissolution, the crystals become smaller and the average lengths of dissolution steps decrease (which leads to a decrease in dissolution rates) and approach the critical value. When dimensions of dissolving crystals is sufficiently reduced, in some cases dissolution is thought to be dynamically stabilized (dissolution suppression) due to a lack of space for active pits/defects formation on the very small crystallite surfaces[41-48]. This phenomenon involves particle-size-dependent critical conditions of energetic control at the molecular level. Although, the authors claim this effect as "a new dissolution model incorporating particle size considerations"[41-48], in fact, they just have introduced some boundary conditions (the minimal pit sizes and crystal dimensions) to the etch pit formation process. One should remind, that a similar effect of the dissolution self-inhibition was detected by the authors of the calcium-rich layer formation model[19,49-53], although the interpretation of this effect was quite different (see above).

Different acids were used in experimental investigations but, unless the conditions of surface coating creation[124], no specific influence of the acids to etch pit formation and growth was found[106-115]. A theoretical basis for the pit formation and growth at the surface outlets of dislocations includes detachment of single ions from the kink sites. The bulk rate associated with dissolution stepwaves arises quite naturally from the equations describing the spreading of step trains from structure defects and densities[43]. However, until recently, the experimental investigations on pits formation and growth on apatites were made when their dimensions became at least 0.3-0.5 μm and even larger. Smaller dimensions of pits were out of the range of old microscopes. That is why, the initial stages of etch pits formation are not quite clear yet.

The investigations on apatite dissolution using atomic force microscopy provided new data on this point[41-48,66,67,118-122]. For example, the growth process of a single pit on apatite was followed since its dimensions were 50 nm[66,67]. Therefore, one may expect new results on even smaller dimensions of pits to appear soon.

Ion exchange model

An ion exchange dissolution model is based on a supposition about adsorption of protons[40] and anions of acid (e.g., citrate anions[125-127]) from a solution onto the surface of apatite and removing ions of calcium and orthophosphate into the solution instead. An uptake of citric acid[125] and citrate ions[126] from dilute (4-12.5 mmol/L for citric acid[125] and 0.05-1 mmol/L for sodium citrate[126]) aqueous solutions by a synthetic HA was found to be time independent and follow *Langmuir* isotherms rather good. However, it was not the case when solutions of higher concentrations were used. In more concentrated solutions (13-100 mmol/L of citrate), this interaction was "reactive" and not "adsorptive"[125].

Adsorption was found to take place by ionic exchange of orthophosphate by citrate ions at the solid-solution interface, caused by a higher affinity of citrate than orthophosphate species for the Ca-sites on the surface. Citrate ions were proposed to interact in two ways: $C_6H_8O_7^{3-}$ interacted weakly in a bi-dentate manner (1 citrate per 2 calcium sites), whereas $C_6H_9O_7^{2-}$ interacted strongly in a mono-dentate manner (1 citrate per 1 calcium site)[126]. Recent computer simulations revealed that this process is followed by hydrogen-bonded interactions of citric acid to surface oxygen ions of apatites[128]. Furthermore, the adsorbed citrate molecules can use their free carboxylate and hydroxyl groups to self-assemble on the HA surface *via* intermolecular hydrogen bonding[129].

Later this model was updated by investigation of apatite dissolution in other acids and an adhesion-decalcification concept was introduced[130,131]. According to this concept, the mechanism of acidic interaction with HA was found to involve two phases. In the first phase, an acid bonds to surface calcium of HA with formation of calcium-acid complexes. Depending on both a solubility and a diffusion rate of the calcium-acid complexes from the HA surface to a solution, the acid will in the second phase either remain attached to the HA surface with only limited decalcification involved or the calcium-acid complexes will detach, resulting in a substantial decalcification effect. Rather similar data, in which carboxylic groups of polyalkenoic acid were adsorbed on the surface of an HA substrate, replaced orthophosphate ions and made ionic bonds with calcium ions of HA, were obtained in another study[132].

Recently, *ab initio* total energy methods were used to study the atomic structure and surface chemistry of HA[133]. All surfaces of HA were found to react strongly with water and a loss of Ca from the surface in exchange for two H appeared to be very favorable. Since these calculations were performed for the case of water adsorption on HA, it remained unclear whether they can be applied to the acidic solutions. Nevertheless, other

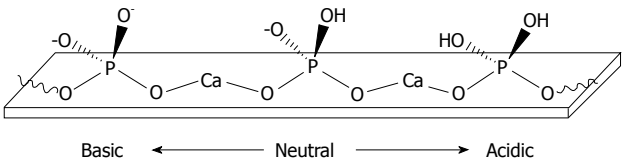


Figure 4 A schematic representation of surface protonation of apatites at different solution pH. Reprinted from Ref. [119] with permission.

researchers found this effect experimentally[86,88]. Furthermore, another type of the exchange was proposed for HA, in which one calcium and one hydroxyl were replaced by one proton[87].

To conclude this model, the time independent ionic exchange of orthophosphate by citrate was detected in dilute solutions only. In more concentrated solutions it transferred into chemical reaction (5) followed by time dependent precipitation of calcium citrate when its solubility was exceeded[125,127]. Application of this model to HA dissolution in other acids revealed its dependency on both the solubility and the diffusion rate of the calcium-acid complexes[130,131]. Thus, new experimental data are necessary, to elaborate the ion exchange model further.

Hydrogen catalytic model

A hydrogen catalytic model is based on a reasonable suggestion about adsorption of protons onto negatively charged oxygen ions of the surface orthophosphate groups of apatites[134]. Sorption of protons results in partial transformation of surface PO_4^{3-} groups into HPO_4^{2-} and catalyses the dissolution process[9,10,15,18,20,53-61,89]. A schematic representation of this process at different solution pH is shown in Figure 4[119]. Besides, recent computer simulations revealed that both OH^- (for HA) and F^- (for FA) located on the surface are protonated as well and, of them, fluoride ions exhibited much lower proton affinities (pK_B = 10.8, a weak base) compared to hydroxide (pK_B = 0, a strong base)[135]. Furthermore, the surface protonation of apatites is intimately related to hydrogen bonding. The details on the latter process are available in literature[136].

One can notice, that the authors of different dissolution models (the diffusion and kinetically controlled[9,10,15,18,20] and polynuclea[56-61] models) have suggested a similar possibility of a catalytic effect of the adsorbed protons. At present, indirect data only are available to support this hypothesis. Namely, at neutral pH, dissociation of ions is penalized by more than 150 kJ/mol giving rise to very stable apatite-water interfaces[135]. This picture changes drastically with decreasing pH, as the protonation of orthophosphate and hydroxide ions lowers the free energy of calcium ions dissociation. An obvious trend in apatite dissolution is that the dissolution rate is increased as the solution pH decreases, which is a general phenomenon observed in dissolution of other minerals. This indicates that dissolution proceeds by surface protonation, which promotes breaking of Ca-O bonds.

In the course of proton uptake, the charge of the surface anions is reduced and the Coulomb attraction to the crystal surface is lowered considerably, which might be considered as "catalysis". Currently, no precise information about a catalytic activity of adsorbed protons on the dissolution of apatites is available. However, it does not mean that this effect does not exist. Up to now, nobody has ever succeeded to reveal a catalytic effect unambiguously due to a lack of an experimental technique able to provide the experimental data necessary. Obviously, the general idea on a catalytic activity of the adsorbed protons seems reasonable and, perhaps, this effect will be better elucidated in future.

SUMMARY ON THE DISSOLUTION MODELS

There is an old tale on six blind men, who wanted to determine what an elephant looked like. An elephant was delivered and the men were allowed to feel different parts of its body. The blind man who felt a leg said the elephant was like a pillar; the one who felt the tail said the elephant was like a rope; the one who felt the trunk said the elephant was like a tree branch; the one who felt an ear said the elephant was like a hand fan; the one who felt the belly said the elephant was like a wall; and the one who felt the tusk said the elephant was like a solid pipe. Thus, six blind men appeared to be in complete disagreement. Then, a wise man explained to them: "All of you are right. The reason every one of you is telling it differently is because each one of you touched the different part of the elephant. So, actually the elephant has all the features you mentioned." The story is widely used to indicate that the reality may be viewed differently depending upon one's perspective, suggesting that what seems the absolute truth may be relative due to a deceptive nature of half-truths.

As the complete physical picture that explains widely observed variations in dissolution behavior is still lacking, a similar approach must be adapted to the aforementioned dissolution models of calcium apatites. Undoubtedly, each from the aforementioned models appears to have limitations and drawbacks of its own and none of them is able to describe the apatite dissolution in general. Moreover, most of the models were elaborated for apatite dissolution in either slightly acidic or nearly neutral ($4 < pH < 8$) aqueous solutions, relatively small values of solution undersaturation and temperatures of 25 ℃ and 37 ℃ only. Nothing is known about the validity of these models for apatite dissolution in strong inorganic acids (HCl, HNO_3, H_2SO_4, H_3PO_4) for solution $pH < 2$ and temperatures above 70 ℃. Moreover, in such "tough" experimental conditions, the numerical value of solution undersaturation by HA and FA becomes uncertain due to impossibility to determine their solubility[1-4]. The latter cases serious problems for application of current versions of calcium-rich layer formation and polynuclear models to apatite dissolution in strong acids, because both models operate with the solution supersatura-

tion/undersaturation phenomena. The abovementioned "tough" dissolution conditions are common in industry of fertilizer production[137] and have to be taken into account by the final version of any dissolution model.

However, there are no doubts that each of the models discussed is correct for the specific experimental conditions studied. The different models are just devoted to diverse aspects of the same process of apatite dissolution and are likely complement each other. Undoubtedly, the dissolution process of calcium apatites has all the features elaborated within eight dissolution models. Unfortunately, it is still impossible to obtain the complete understanding for all the processes involved because experimental techniques able to provide direct following after diffusion, sorption, detachment and transformation of the single atoms, ions and molecules currently are lacking. Therefore, researchers are still forced to make conclusions about the events happening at the atomic (ionic) level based on indirect measurements and/or calculations only. That is why, combining the experimental and theoretical findings, obtained by different investigators (often under hardly comparable experimental conditions), currently, seems to be the only way to create a general depiction of the dissolution mechanism of calcium apatites in acids.

A REASONABLE CLASSIFICATION OF THE DISSOLUTION MODELS

At the fundamental level reactions between solids and liquids involve a coupled sequence of mass transport, adsorption/desorption phenomena, heterogeneous reaction, chemical transformations of intermediates, *etc.*, whose identification, separation and kinetic quantification are all necessary if the mechanism of the process is to be fully understood and described[138]. It is also generally agreed that during dissolution lattice ions undergo the following processes: (1) detachment from a kink site, (2) surface diffusion away from the crystal steps, (3) desorption from the surface and (4) diffusion into the bulk solution[139]. Therefore, the steady-state conditions of apatite dissolution in aqueous acidic media include the following simultaneous processes or steps: (1) diffusion of chemical reagents (H^+ and anions of acid A^{n-}) from bulk solution to the solid/liquid interface; (2) adsorption of the chemicals onto the surface of apatite; (3) chemical transformations on the surface; (4) desorption of products (ions of fluoride, calcium and orthophosphate) from the crystal surface; and (5) their diffusion into the bulk solution.

All the steps mentioned above are likely to be much more complicated. For example, processes 1 and 5 include chemical transformations happen with the ions during diffusion, because solution pH is known to depend on the distance from the solid/liquid interface (in acidic solutions it is higher near the surface of apatite and decreases when the distance increases)[140,141]. Processes 2 and 4 include ionic diffusion along the surface both to (step 2a) and away from (step 4a) the crystal steps, respectively, as well as a diffusive jump (steps 2b and 4b)[139]. Finally, process 3 consists of several successive chemical transformations [step 3a - chemical equations (1)-(4)][100-102] and includes ionic detachment from the kink sites (step 3b)[139]. Moreover, for adsorption (step 2) to take place, the following intermediate steps are necessary: (1) dehydration of a surface site; (2) partial dehydration of ions; and (3) a diffusive jump toward the surface[139]. One can also expect three similar intermediate steps (diffusion jump from the surface, hydration both the ions and the surface site) for desorption (step 4).

As shown above, different models describe just diverse aspects of the same phenomenon of apatite dissolution. Commonly, the main distinction is made between the transport control and surface-reaction control. For example, in the diffusion controlled, two-site and polynuclear models steps 1 and 5 limit a reaction rate. On the contrary, in the kinetically controlled, chemical and hydrogen catalytic models a reaction rate is limited by step 3. In the cases of the ion exchange and self-inhibition (or calcium-rich layer formation) models, a reaction rate is likely to be controlled by both ionic diffusion (steps 1 and 5) and kinetics of the adsorption/desorption phenomena (steps 2 and 4). Processes of etch pit formation and dissolution stoichiometry - are the experimental facts, not models. Thus, they may be controlled by factors pertaining to any step from 1-5 and even all of them.

BRIEF INFORMATION ON APATITE STRUCTURE

Briefly, crystals of HA and FA consist of individual orthophosphate tetrahedra linked by calcium cations. The orthophosphate groups forms the skeleton having two types of calcium sites. The first [Ca(1) site] is occupied by four calcium atoms that have a nine-fold coordination, while the second [Ca(2) site] is occupied by six calcium atoms having a seven-fold coordination. Fluoride (for FA) or hydroxide (for HA) anions are located within the same channels as the Ca(2) sites and have a high mobility[1-4,142,143]. Thus, the apatite structure contains Ca-F (for FA), O-H (for HA), Ca-O and P-O bonds; consideration of the relative electrostatic strength of these bonds suggests that their relative destruction rate is consistent with: Ca-F ≈ Ca-OH > Ca(1)-O > Ca(2)-O > P-O. Considering its structure, once all Ca-F and Ca-O bonds are broken, apatite is destroyed; while breaking of P-O bonds is unnecessary for apatite dissolution[96].

NECESSARY ASSUMPTIONS AND LIMITATIONS

When apatite comes into a contact with an acidic aqueous solution, dissolution steps 1-5 (see section 4) begin. Before giving the detailed description of the processes involved, the following assumptions and limitations must

be made: (1) the stoichiometric apatite (Ca/P = 1.67) is dissolved and neither non-stoichiometric layers nor other ions except of calcium, orthophosphate, hydroxide (for HA) or fluoride (for FA) are initially present in the crystal lattice, whereas volume and surface defects (dislocations and dislocation outlets respectively) might be present and, if present, they are distributed randomly; (2) except of the presence of dislocation outlets, the initial surface of apatite is perfect (molecularly sooth). Otherwise, each imperfection might act as a possible dissolution nucleus; (3) in spite of the limitations and drawbacks discussed above, all the afore-discussed dissolution models are correct and complementary to each other; (4) in some cases, anions of acid might have an influence on apatite dissolution due to a specific affinity (e.g., citrate) or by means of formation of insoluble compounds (e.g., sulfate, fluoride). That is why, anions are specified neither here nor below. It is just assumed that dissolution of apatite occurs in acid H_nA, where A^{n-} is an anion; (5) only soluble compounds are formed during the apatite dissolution in acids. No precipitates are obtained; (6) hydration effects for all the ions and molecules involved as well as those for crystal surface of apatite[99,144-148] are omitted for simplicity; (7) all crystal faces of a solid apatite are equal and have a similar ionic arrangement. Although, it was found that HA (001) facets could be more resistant against acidic dissolution than (100) ones[149], no specific influence of different crystal faces on the dissolution process is considered; and (8) since the afore-described dissolution models have been elaborated for micron-sized apatite crystals, while the nanodimensional calcium orthophosphates possess the special properties[150,151], to eliminate the size effects, dissolution of large crystals is described. No specific influence of crystal dimensions on the dissolution mechanism is considered.

Based on these assumptions and limitations, an attempt to create the general description of the apatite dissolution mechanism at the atomic (ionic) level is given below.

CREATION OF THE GENERAL DISSOLUTION MECHANISM

Atomic (ionic) description for the perfect crystals

Immediately after being placed to acidic aqueous solutions, the surface of apatite crystals becomes in contact with water molecules and ions of the acid, which results in sorption of all these chemicals with simultaneous formation of a solid/liquid interface and various adjacent strata, such as a Nernst diffusion layer, an electrical double layer, *etc*. Transport of the chemicals (H^+ and A^{n-}) to the solid/liquid interface always happens by ionic diffusion through the Nernst diffusion layer (Figure 1). A thickness of this layer depends on both solution hydrodynamics and dimensions of the crystals dissolving: it decreases when agitation intensity increases and crystal sizes decrease. However, in no cases the thickness becomes equal to the zero[152]. Thus, a concentration gradient is always present near the solid/liquid interface, the diffusion laws always remain valid and all findings of the diffusion-controlled model (e.g., an adsorption resistance and a diffusion jump) remain applicable for any case of apatite dissolution. A similar approach is correct for the surface phenomena: when dissolution occurs, adsorption and desorption of ions, as well as chemical transformations (1)-(4) always take place on the surface regardless the experimental conditions chosen.

After being delivered by diffusion to the solid/liquid interface, ions of H^+ and A^{n-} are adsorbed onto the surface of apatite. A great number of various surface complexes might be formed as a result[86-89,153-155]. According to the diffusion-controlled model, there is an adsorption resistance for ions to be adsorbed onto the surface and in order to overcome the resistance the ions make a diffusive jump toward the surface to a distance corresponding to their size[139,156]. Being charged positively, protons are adsorbed onto oxygen ions of orthophosphate groups[58] as well as onto ions of fluoride (in the case of FA) and hydroxide (in the case of HA). After the model by Wu *et al*[153], the surface protonation of apatites proceeds *via* formation of ≡POH surface groups ("≡" stands for the surface) at $5 < pH < 7$, while apatite surfaces become fully protonated at $pH < 5$. One may expect to find some differences in the adsorption kinetics of protons onto fluoride, hydroxide and orthophosphate ions. Namely, due to a higher electro negativity of fluoride (when compared to oxygen ions of orthophosphate groups) and a higher basicity of hydroxide (when compared to orthophosphate), adsorption of protons might happen faster (or previously) onto these ions when compared with orthophosphate. However, recent results of computer simulations indicated a possibility of OH^- protonation by the nearest HPO_4^{2-} ion[135], indicating to the fact, that orthophosphate ions might be protonated faster (or previously) if compared to that for hydroxide ions. Obviously, this topic needs to be clarified in future.

Anyway, negatively charged anions A^{n-} may be adsorbed onto calcium cations only. According to the ion exchange model, the exchange process shows an adsorption of about one anion per unit-cell of apatite[125-127]. On the other hand, the surface of apatites is charged positively in aqueous acidic media and negatively in basic solutions (the point of zero charge is at solution pH within 6.8-8.5) with an electric double layer formation at the solid/liquid interface[70-72,78,86-88,153-155,157,158]. The latter points out to a non-equivalent ionic adsorption of H^+ and A^{n-} onto apatite: in acidic solutions, adsorption of protons always exceeds that of A^{n-}, while in basic solutions the situation is opposite. Therefore, in acidic solutions there is at least one extra-adsorbed proton per several neighboring unit-cells of apatite when compared to the number of adsorbed anions. The fact of a non-equivalent ionic adsorption might be explained by differences in sizes and mobility between H^+ and A^{n-}[159]. Great difference in the surface sites available is another reason for the non-equivalent ionic adsorption. Namely,

the concentration of the lattice ions being on the surface of HA were found to be equal to 2.57, 3.02 and 4.50 ions/nm^2 for OH^-, PO_4^{3-} and Ca^{2+}, respectively[69]. Furthermore, according to drawings of the apatite structure, the most part of its surface (up to 80%-90%) is covered by oxygen ions of orthophosphate groups[160].

Ions of the crystal lattice of apatites are known to have different crystallographic positions: so-called X-ions (F^-, OH^-, Cl^- and substitutes for them) are located in Ca(2) channels parallel to *c*-axis[1-4,142,143]. This position results in a relatively high mobility of X-ions: for example, they might be mutually substituted rather easily [88,89,161-163] with formation of intermediate compounds, like fluorhydroxyapatites or hydroxyfluorapatites[17,83,164]. Based on these findings, dissolution of apatite in acids was suggested to start with detachment of X-ions (more likely, as HX) from the surface[100-102] followed by their diffusion away from the crystal steps and further into the bulk solution[139,156]. Recent computer simulations revealed some differences in the dissolution kinetics between F^- and OH^- anions in apatites: surface fluoride is dissolved not as readily as hydroxide is[143]. Initial leaving of X-ions was also detected in the incongruent dissolution model[17,68,77,83,88,89]. Moreover, numerical values for the surface tension found for dissolution of HA appeared to be clearly lower than those found for HA growth (the polynuclear model). The latter data were explained by partial protonation of orthophosphate groups and missing of some hydroxide ions on the crystal surface[60].

After detachment of X-ions from the surface, there are calcium, orthophosphate, H^+ (as HPO_4 and/or H_2PO_4 groups) and A^{n-} ions left on it (hydration effect is omitted for simplicity). From now on, any differences between FA and HA disappear. In any cases, adsorption of protons onto calcium is impossible due to charge repulsion. Therefore, an electrical double layer with a positive charge on apatite cannot be continuous at the atomic (ionic) scale. There should be local uncharged places in it, say, at the positions of calcium cations. According to the chemical model, an interaction between calcium cations and anions of acid adsorbed from a solution is believed to happen in such places[100-102]. This interaction results in breaking of surface ≡O-Ca bonds ("≡" stands for the surface) and detachment of some calcium from the kink sites followed by their diffusion away from crystal steps and further into the bulk solution (the diffusion-controlled model[139,156]). Detachment of calcium might occur as calcium-acid complexes (the ion exchange model). Recent computer simulations revealed that a local excess charge of +3 and +4 must be created to cause exothermic Ca^{2+} displacement from Ca(1) and Ca(2) cites, respectively[135]. If so, under otherwise equal conditions, detachment of Ca^{2+} ions from Ca(1) cites of the apatite surface should happen faster and/or easily than that from Ca(2) cites.

Detachment of calcium ions results in formation of dissolution nuclei. These nuclei are defined as collections of vacant sites for Ca^{2+}, PO_4^{3-} and X^- ions on the crystal surface of apatite[56]. According to the polynuclear model, removal even of one ion might result in further dissolution because critical nuclei (x*) were calculated to consist of 1-26 ions for dissolution of HA and 0.3-34 ions for dissolution of FA. (According to the authors, $x^* < 1$ means that there is no nucleation barrier to be overcome[61]. Since one unit cell of apatite contains 18 ions, $x^* > 18$ means that more than one unit cell should be dissolved for a nucleus to form). The numeric values for x* were found to depend on solution pH and solution undersaturation[60,61]. Furthermore, due to charge repulsion, adsorbed protons (as HPO_4 and/or H_2PO_4 groups) might catalyze detachment of calcium ions from the kink sites (the hydrogen catalytic model).

After being detached, calcium cations [possibly, as calcium-acid complexes (the ion exchange model)] diffuse along the surface away from the dissolution steps before entering the solution[139]. For dissolution of octacalcium phosphate (OCP): $[Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O]$ in slightly acidic (pH = 5.66) solutions numeric values for the mean surface diffusion distance of the lattice ions detached from steps were calculated. These values were found to depend on the edge free energy and be within $(17 \pm 4)\alpha - (41 \pm 10)\alpha$, where $\alpha \approx 3.7$ Å is the size of a growth unit (or mean ionic diameter)[156]. Numeric values of mean ionic diameter for apatites were also calculated. They appeared to be less than that for OCP: 3.09 Å for HA and 3.07 Å for FA[62]. Taking into the consideration great similarities found between the chemical composition and crystal structures of OCP and HA[165], one might assume that the numerical values of surface diffusion distance for HA should be close to the values for OCP.

Ionic detachment of some calcium results in removing of a local positive charge from apatite, which is immediately compensated by adsorption of other protons from the acidic solution. This conclusion is based on the surface charge measurements: no information on influence of dissolution time to values of the surface charge on apatite has been found in literature[70-72,78,86-88,153-157]. So, one may assume, that if a chemical composition of the solution is kept constant the surface charge on apatite will also remain constant during dissolution. Replacement of calcium by protons results in formation of mono-atomic layer acidic calcium orthophosphates on the crystal surface. Chemical phenomena of these transformations are described by the chemical model[100-102] and the kinetics (it strongly depends on the experimental conditions chosen) - by the surface controlled model.

After being desorbed from the surface, calcium cations (presumably, coupled with anions A^{n-}) diffuse through the Nernst layer into the bulk solution (the diffusion controlled model)[139,156]. However, according to the calcium-rich layer formation model, a part of the already dissolved calcium ions might be adsorbed back onto apatite. Adsorption of calcium was suggested to happen at the very beginning of dissolution only and resulted in formation of a perm-selective layer of calcium cations with or without counter ions (A^{n-} and/or

acidic orthophosphate)[19,49-53,68]. In this case, there should be a competition between protons and calcium cations for the exposed ions of oxygen on the surface to be adsorbed onto. Experimental data on a shift of the point of surface zero charge into more basic solution pH in presence of calcium in a solution[157] are in favor of such competition.

An idea on formation of some layer on the surface of apatite was raised in several dissolution models. For example, there is either a supposition (the polynuclear, diffusion and kinetically controlled models) or a description (the ion exchange, hydrogen catalytic and chemical models) of a very thin virtual layer of acidic calcium orthophosphates (more exactly presence of HPO_4^{2-} ions) on the surface of apatite. Besides, according to the calcium-rich layer formation model, dissolution of apatite happens by ionic diffusion through a layer containing calcium with or without counter ions[19,49-53,68]. In part, this idea can be found within the ion exchange model where a monolayer of calcium citrate[125-127] and/or calcium-acid complexes[130,131] are assumed to form onto apatite during dissolution. However, no other model requires such suggestion. According to the rest of them, formation of any calcium containing compounds (different from acidic orthophosphates) on apatite is not discussed at all.

According to the chemical model, the initial stages of apatite dissolution consist of calcium detachment from the surface and incorporation of protons instead. Orthophosphate groups are assumed to keep their positions without any relocation[100-102]. Due to the fact, that calcium occupies definite lattice positions, whereas protons are bound to oxygen ions of orthophosphate groups, removing of each calcium results in decreasing of attraction forces between the nearest (to this calcium) orthophosphate group and rest part of the crystals. When all (or almost all) neighboring cations of calcium have been removed, orthophosphate groups (as $H_2PO_4^-$, $CaH_2PO_4^+$ or H_3PO_4 - it is not clear yet) also detach from the surface. Then they diffuse along the surface away from the dissolution steps before entering the solution as described above for calcium[139,156].

In the case of crystal faces with perfectly smooth surface (dissolution steps are absent), detachment of one or several ions results in formation of dissolution nuclei, which the polynuclear model is based on[55-63]. According to this model, all sites in nuclei edges are the kink positions[62] and, after appearance, the nuclei grow and spread over the surface with a definite lateral rate[56], giving rise to formation of dissolution steps. If dissolution steps already existed on the crystal faces of apatite, detachment of one calcium or one orthophosphate would result in dissolution step movement jump-wise over a distance equal to the sizes of these ions (approximately for 1 and 3 Å, respectively).

The latter is also valid for dissolution of crystal edges and corners. Since the classical paper by Kaischew[166], it is generally considered, that ions are less strongly bound along edges of a crystal than in the middle of faces and still less strongly at the corners[167]. No information about the ionic arrangements on edges and corners of apatite crystals has been found in literature. Therefore, two boundary conditions are possible: the edges and corners mainly consist of ions of either calcium or orthophosphate. However, the edges parallel to the *c*-axis, in principle, may consist of X-ions (F^-, OH^-, Cl^-). The last case is the simplest one. According to the chemical model[100-102], dissolution of apatite starts with protonation and detachment of X-ions, followed by removing of calcium (one should remind here that "walls" of the channels where X-ions are located consist of Ca(2) ions[96]) and afterwards by protonation and removing of orthophosphate. In the case, when the edges and corners of apatite mainly consist of calcium, again, according to the chemical model, detachment of weakly bounded calcium precedes protonation and removing of orthophosphate. Finally, if the edges and corners mainly consist of orthophosphate, the dissolution will start by chemical interaction of protons with these weakly bounded orthophosphate groups. The latter decreases electrostatic attraction forces between orthophosphate anions and neighboring calcium cations (attraction forces between Ca^{2+} and PO_4^{3-} are evidently stronger when compared with those between Ca^{2+} and HPO_4^{2-}). These forces become still weaker after adsorption of the second proton onto the given orthophosphate anion, causing its transformation to $H_2PO_4^-$ followed by detachment.

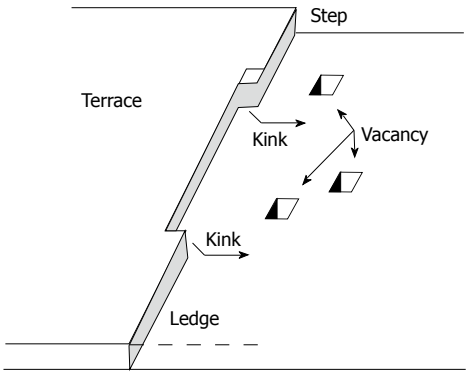


Figure 5 Surface of a crystal according to Kossel[168]. The various types of imperfections are shown. Reprinted from Ref. [34] with permission.

Influence of dislocations and surface defects

Before now, no data on crystal defects have been used. For this reason, the above description is valid for dissolution of the perfect single crystals without defects and with the molecularly smooth surface. However, like other solids, crystals of apatite always contain both surface irregularities (e.g., steps, missing ions and dislocation outlets) and structural defects inside the bulk of crystals (e.g., dislocations and inclusions). The schematic depiction of a crystal surface is shown in Figure 5. This model is known as the "Kossel model"[168]. In principle, any surface irregularities may act as dissolution nuclei

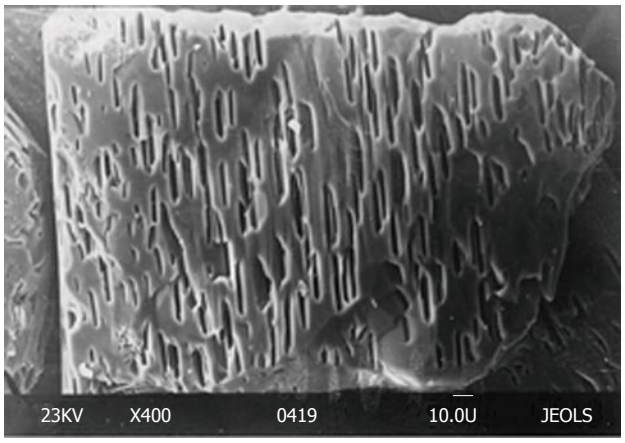


Figure 6 An example of etched crystal surface of natural fluorapatite with typical hexagonal etch pits. Bar 10 μm.

because sometimes even one missing ion might become the critical nuclei (the polynuclear model)[60,61].

Each dislocation outlet on apatite was found to be a hollow core with radius within 8.3-20 Å for the screw dislocations and even 18-43 Å for the edge ones[109]. Dimensions of the hexagonal unit-cell of apatite are: $a \approx 9.43$ Å, $c \approx 6.88$ Å. If the numeric values for the dislocation outlets were calculated correctly, their dimensions (diameter of the hollow cores) would be 1.8-4.2 times a or 2.4-5.8 times c (for the screw dislocations) and even 3.8-9.1 times a or 5.2-12.5 times c (for the edge dislocations). Thus, each dislocation outlet on the crystal surface looks like a large dissolution nucleus equal to detachment of 3-19 unit cells, (if this is taken to be the product ac) for the screw dislocations and even of 15-90 unit cells for the edge ones.

The process of etch pits formation and growth on apatites was described in details elsewhere[41-48,66,67,106-122]. In the case of single crystals of pure HA, an acid attack was found to start formation of one etch pit in the basal plane which was the preferred dissolution spot or active site. Immediately afterwards the acid formed a longitudinal hole parallel to the c-axis[110]. On the contrary, dissolution of natural FA was found to happen with formation of a great number of etch pits (about 5×10^5 cm^{-2}) on the surface (Figure 6)[113-115]. The latter just points out to the great differences in amount of crystal defects and impurities between the chemically pure[41-48,66,67,106-112,118-122] and natural[113-115] apatites.

In any case, after being formed, the pits were found to grow in all directions (length, width and depth - see Figure 3) with definite rates until they either covered all crystal faces of apatite (dissolution of natural crystals[113-115]) or made longitudinal holes parallel to the c-axis (dissolution of the single crystals of pure HA[106-111]). However, according to "a new dissolution model incorporating particle size considerations", the dissolution process becomes spontaneous only when the pits are reached the critical sizes[41-48]. The unit-step movement of etch pit growth was suggested to consist of removing of a single ion, followed by surface diffusion away from the place of ionic detachment, desorption from the surface and diffusion into the bulk solution. All these processes evidently occur according to the basic findings of the ion exchange, chemical, calcium-rich layer formation, hydrogen catalytic and diffusion controlled dissolution models.

To conclude this part, except the dissolution rates increasing and surface etching, no other influences of dislocations on the dissolution mechanism were found.

CONCLUSION

Thus, based on eight dissolution models drawn from the previously published papers, an attempt to create the general description of apatite dissolution process at the atomic (ionic) level has been made. This dissolution mechanism is based on current level of knowledge and will be updated, corrected and modified simultaneously with appearance of new experimental data. Now some missing and unclear points to be investigated in future can be outlined: (1) chemical transformations happening with all ions during diffusion through the Nernst layer; (2) chemical composition of the apatite surface during dissolution; (3) processes of ionic sorption and detachment; (4) processes of dissolution nuclei formation and growth; (5) initial stages of etch pits formation at the dislocation outlets; and (6) specific influence of anions to the ionic sorption, surface diffusion and detachment. The above topics should be investigated in order to have better understanding of all the processes involved. For example, atomic force microscopy and phase shift interferometry might be useful tools in investigations on dissolution nuclei and etch pits formation[66,67]. Micron-sized (better nano-sized) electrodes might be helpful in studying ionic transformations during diffusion through the Nernst layer[140]. Modern techniques of the surface state analysis might be helpful in understanding the surface structure and its chemical composition.

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Miami, FL, United States

January 26, 2012
Symposium of the Swiss Society of Pharmacology and Toxicology, Advances in Pharmacology - Cardiovascular Pharmacology
Bern, Switzerland

January 28 – February 1, 2012
LabAutomation2012
Palm Springs Convention Center, Palm Springs, CA, United States

February 1-4, 2012
3rd International Workshop on Medical Image Analysis and Description for Diagnosis System
Hotel Tivoli Victoria, Algarve, Portugal

February 24, 2012
State Stem Cell Agency Governance Subcommittee
San Francisco, CA, United States

March 11-14, 2012
Thoracic Imaging 2012
Hyatt Regency, Huntington Beach Resort and Spa, Huntington Beach, CA, United States

March 25-30, 2012
44th International Diagnostic Course Davos (IDKD)
Davos, Switzerland

April 26-29, 2012
75th Anniversary of the Canadian Association of Radiologists Annual Scientific Meeting
Le Centre Sheraton, Montreal, Quebec, Canada

April 29 - May 4, 2012
EUCHEM Conference on Stereochemistry
Brunnen, Switzerland

May 4-6, 2012
World Congress on Biotechnology
Hyderabad, India

June 7-9, 2012
ASCI 2012 - 6th Congress of Asian Society of Cardiovascular Imaging
Bangkok, Thailand

June 9-13, 2012
2012 Annual Meeting of the Society of Nuclear Medicine
Miami Beach, FL, United States

August 15-19, 2012
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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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Both personal authors and an organization as author

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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BRIEF ARTICLE

Factors influencing teamwork and collaboration within a tertiary medical center

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Abstract

AIM: To understand how work climate and related factors influence teamwork and collaboration in a large medical center.

METHODS: A survey of 3462 employees was conducted to generate responses to Sexton's Safety Attitudes Questionnaire (SAQ) to assess perceptions of work environment via a series of five-point, Likert-scaled questions. Path analysis was performed, using teamwork (TW) and collaboration (CO) as endogenous variables. The exogenous variables are effective communication (EC), safety culture (SC), job satisfaction (JS), work pressure (PR), and work climate (WC). The measurement instruments for the variables or summated subscales are presented. Reliability of each sub-scale are calculated. Alpha Cronbach coefficients are relatively strong: TW (0.81), CO (0.76), EC (0.70), SC (0.83), JS (0.91), WP (0.85), and WC (0.78). Confirmatory factor analysis was performed for each of these constructs.

RESULTS: Path analysis enables to identify statistically significant predictors of two endogenous variables, teamwork and intra-organizational collaboration. Significant amounts of variance in perceived teamwork (R^2 = 0.59) and in collaboration (R^2 = 0.75) are accounted for by the predictor variables. In the initial model, safety culture is the most important predictor of perceived teamwork, with a β weight of 0.51, and work climate is the most significant predictor of collaboration, with a β weight of 0.84. After eliminating statistically insignificant causal paths and allowing correlated predictors1, the revised model shows that work climate is the only predictor positively influencing both teamwork (β = 0.26) and collaboration (β = 0.88). A relatively weak positive (β = 0.14) but statistically significant relationship exists between teamwork and collaboration when the effects of other predictors are simultaneously controlled.

CONCLUSION: Hospital executives who are interested in improving collaboration should assess the work climate to ensure that employees are operating in a setting conducive to intra-organizational collaboration.

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Key words: Teamwork; Intra-organizational collaboration; Safety culture; Work climate in a hospital

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INTRODUCTION

Change efforts such as total quality management and continuous quality improvement reveal the importance of teamwork and collaboration to organizational success. In health care, teamwork has consistently been shown to improve the quality of health care and reduce medical errors[1,2]. In addition, Hoegl and Gemuenden[2] demonstrated that the quality of the teamwork is significantly associated with team performance on innovative projects, which indicates that teamwork is crucial to organizational growth and development. Both of these studies showed that communication is of the utmost importance for determining teamwork and collaboration. This paper uses path analysis to construct a causal path model which helps identify intra-organizational factors influencing the variation in perceived teamwork and collaboration within a large medical center.

MATERIALS AND METHODS

Literature review

Teamwork is viewed as group members working together to accomplish a common goal. The key insight is that team members must possess a mutual awareness (i.e., shared perceptions about communication, safety culture, work climate and work pressure), which enables them to interact, anticipate each other's actions and needs, and carry out team processes like coordination. In recent years, organizational collaboration has begun to emerge as a distinct focus of scholarly and empirical research[3]. Understanding employees' perceptions of an organization has become increasingly important in recent years. Collaboration is defined as "to work jointly with others or together especially in an intellectual endeavor"[4]. Thomas *et al*[3] defined inter-organizational collaboration as a term used by scholars and practitioners to describe a process that can emerge as organizations interact with one another to create new organizational and social structures. The amount of research on inter-organizational collaboration could fill many volumes[5]. However, the amount of research on its counterpart, intra-organizational collaboration, pales by comparison. The discrepancy may reflect the longstanding precedence of the inter-organizational view in organizational research[3]. However, in recent years, intra-organizational views begun to gain attention[5]. These views focus more on the organizational relationships within a specific organization rather than on those that form outside the organization[5]. In particular, the collaboration among employees within an organization can be just as important as, if not more important than the collaboration between organizations. This paper will pursuit the former view and quantitatively assesses a path analysis model of predictors of intra-organizational collaboration.

With respect to demographics, research has indicated the women tend to be more collaborative than men, which is why women who work in environments requiring high levels of teamwork often excel in leadership positions[6]. Gellers and Kuipert[7] demonstrated that age also is positively related to teamwork; as the average age of team members increases, so too does the quality of the group's work.

Research questions and hypotheses

Given the obvious importance of teamwork and collaboration in organizations, the central question in this study is to what degree work climate, work pressure, perceptions of safety, job satisfaction, and communication are significant determinants of teamwork and collaboration. Various organizational research articles have provided the basis for the theoretical framework used to develop the study hypotheses[8-15]. The exogenous variables in this study are Effective Communication (EC), Safety Culture (SC), Job Satisfaction (JS), Work Pressure (PR), and Work Climate (WC). The endogenous variables are teamwork (TW) and collaboration (CO). Each of the five exogenous variables is hypothesized to exert influence independently on the two endogenous variables. The study assumes that teamwork predicts collaboration.

Methodology

Data were gathered from a sample selected in 2008 that consists of 3462 employees working for the same tertiary medical center in Taipei, Taiwan. Participants were asked to respond to Sexton's[16-18] Safety Attitudes Questionnaire (SAQ) to assess perceptions of work environment via a series of five-point, Likert-scaled questions. This questionnaire was translated and piloted tested as part of the large survey conducted in the facility.

The exogenous variables are effective communication (EC), safety culture (SC), job satisfaction (JS), work pressure (PR), and work climate (WC). The endogenous variables are teamwork (TW) and collaboration (CO). Teamwork is measured by responses from six related questions in regard to employees' perceived acceptance of any suggestions, opportunities for expressing concerns with care problems, ability to solve clinical problems together, provision of patient support collectively, ability to engender collegial responses, and partnership between physicians and nurses as a well-coordinated team. Collaboration is operationally defined as physicians, nurses, and other clinical staff who work collaboratively within the medical center. The measurement instruments for the variables or summated subscales are presented in Table 1. Reliability of each sub-scale was calculated. Alpha Cronbach coefficients are relatively strong: TW (0.81), CO (0.76), EC (0.70), SC (0.83), JS (0.91), WP (0.85), and WC (0.78).

Table 1 Variables, questions, and constructs for the analysis

Construct	Question or statement[1]
Communication effectiveness (CE)	
	It is easy for personnel here to ask questions when there is something that they do not understand
	I know the proper channels to direct questions regarding problems encountered at work
	I receive appropriate feedback about my performance
	My suggestions about safety issues would be acted upon if I expressed them to management
Teamwork (TW)	
	Staff input is well received in the work area
	If it is difficult to speak up if I perceive a problem in the work setting
	Disagreements in the work setting are resolved appropriately
	I have the support I need from other personnel
	The professional staff here work together as a well-coordinated team
Safety culture (SC)	
	I would feel safe being taken care of in my work area
	Errors or mistakes are handled appropriately in the work area
	It is very difficult to discuss errors or mistakes at work
	I am encouraged by my colleagues to report any concerns I may have
	The culture here makes it easy to learn from the errors of others
Job satisfaction (JS)	
	I like my job
	Working here is like being part of a large family
	This is a good place to work
	I am proud to work in this place
	Morale here is very high
Work pressure (WP)	
	When my workload becomes excessive, my performance is impaired
	I am less effective at work when fatigued
	I am more likely to make errors in tense or hostile situations
	Fatigue impairs my performance during emergency situations
Collaboration (CO)	
	I experience good collaboration with other nurses
	I experience good collaboration with physicians
	I experience good collaboration with other health professionals
Work climate (WC)	
	Problem personnel are dealt with constructively by management
	This hospital does a good job of training new personnel
	All the necessary information for diagnostic and therapeutic decisions is routinely available to me
	Trainees in my discipline are adequately supervised

[1]Likert scale was used for each question: Disagree strongly (1); disagree slightly (2); neutral (3); agree slightly (4); and agree strongly (5). Subscales were constructed by summing the relevant items under the respective constructs.

Table 2 Descriptive statistics for the study variables (n = 3467 employees)

	EC	SC	JS	PR	WC	TW	CO
Mean	3.38	3.69	3.76	3.76	3.55	3.76	3.69
Standard deviation	1	0.66	0.89	0.9	0.62	0.71	0.71

EC: Effective communication; SC: Safety culture; JS; Job satisfaction; PR: Work pressure; WC: Work climate; TW: Perceived teamwork; CO: Collaboration.

Table 3 Correlation matrix for the study variables

	EC	SC	JS	PR	WC	TW	CO[2]
EC	1.00						
SC	0.33[1]	1.00					
JS	0.26[1]	0.66[1]	1.00				
PR	-0.13[1]	-0.04[1]	-0.13[1]	1.00			
WC	0.47[1]	0.68[1]	0.61[1]	-0.06[1]	1.00		
TW	0.37[1]	0.72[1]	0.61[1]	-0.06[1]	0.67[1]	1.00	
CO	0.31[1]	0.58[1]	0.52[1]	-0.03	0.86[1]	0.62[1]	1.00

[1]Statistically significant at 0.01 or less, [2]Endogenous variable. EC: Effective communication; SC: Safety culture; JS; Job satisfaction; PR: Work pressure; WC: Work climate; TW: Perceived teamwork; CO: Collaboration.

Confirmatory factor analysis was performed for each of these constructs. Similar results on psychometric properties as documented in previous studies[19-21] were found. The confirmatory factor analysis results of this study could be obtained from the authors at request.

To analyze the causal relationship among these variables, a path analysis model was developed using the five exogenous variables as predictors and the two endogenous variables as the outcome measures. It is postulated that teamwork positively affect intra-organizational collaboration. Age and gender are considered control variables (Table 1).

RESULTS

Table 2 shows the summary statistics for each of the study variables measured by the average of a summative scale, ranging from 1 (strongly disagree) to 5 (strongly agree). As far as demographics of the hospital employees are concerned, the descriptive analysis showed that 81.4 % of the sample were females and 18.6 % were males. Younger individuals outnumber older individuals (65.1% of the sample was under the age of 40 years). Although all exogenous variables are significantly correlated, no strong multicollinearity exists (Table 3). Thus, no predictor variables were excluded from the analysis. The correlation between teamwork and collaboration is 0.62.

In the initial analysis, effective communication (EC), safety culture (SC), job satisfaction (JS), work pressure (PR) and work climate (WC) were considered as predictors of perceived teamwork and collaboration. The total variance in teamwork accounted for by the five predictors is 40%, whereas the total variance in collaboration

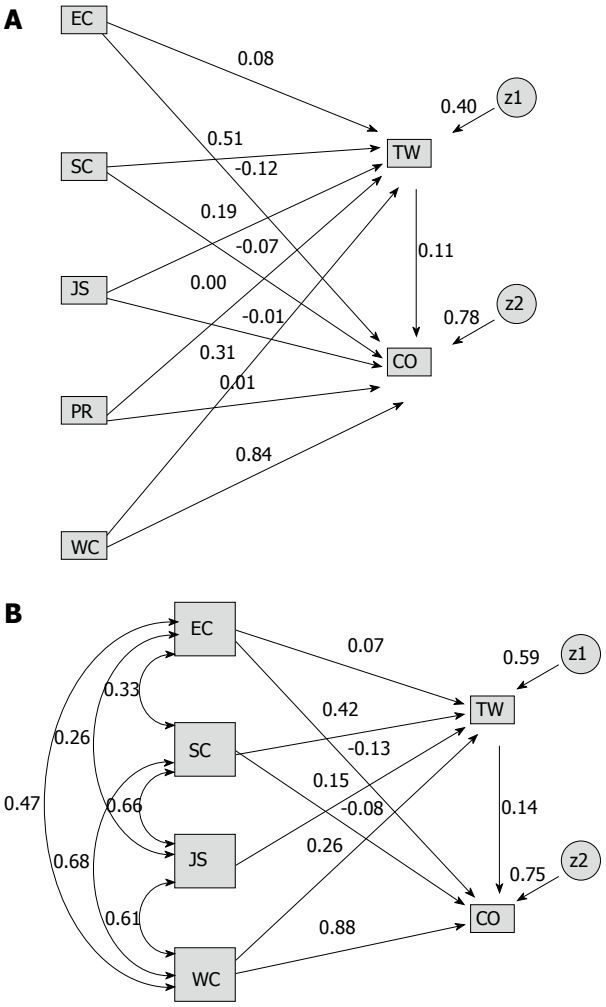


Figure 1 Path analysis and revised path analysis (B) of predictors for perceived teamwork and collaboration. Teamwork (TW); collaboration (CO); effective communication (EC); safety culture (SC); job satisfaction (JS); work pressure (PR); and work climate (WC).

accounted for by five predictors and teamwork is 78% (Figure 1A). However, work pressure is not significantly related to teamwork. Work pressure and job satisfaction are not significantly related to collaboration. Finally, teamwork is significantly but weakly related to collaboration (β = 0.11) when the effects of other predictors are simultaneously controlled.

A revised path analysis that includes only statistically significant predictors of perceived teamwork and collaboration as well as intercorrelations among the predictor variables is presented in Figure 1B. This model accounts for 59% of variance in teamwork and 75% of variance in collaboration. Teamwork remains weakly and positively correlated with collaboration (β = 0.14).

Gender and age were considered as control variables in the primary analysis of perceived teamwork and collaboration. However, gender was found not to be a statistically significant factor to explain the variation in teamwork. Age was found to be negatively correlated with teamwork, in contrast to previous research[6] has demonstrated just the opposite relationship.

Table 4 Regression statistics of the revised path analysis

Predictor variables	Standardized regression coefficients	Unstandardized regression coefficients	Standard errors	Critical values
SC→TW	0.42	0.45	0.02	25.46[1]
JS→TW	0.15	0.12	0.01	9.39[1]
WC→TW	0.29	0.33	0.02	18.47[1]
EC→CO	-0.13	-0.09	0.01	-13.53[1]
TW→CO	0.10	0.10	0.01	8.55[1]
WC→CO	0.85	0.98	0.01	69.04[1]

[1]Statistically significant at 0.01 or less. Goodness of fit (GOF) statistics for the structural equation model: χ^2 = 69.44 with 3 degrees of freedom; CMIN/Γ = 23.15, *P* = 0.001; NFI index = 1.00; CFI index = 0.995; and root mean squares error = 0.08. EC: Effective communication; SC: Safety culture; JS: Job satisfaction; PR: Work pressure; WC: Work climate; TW: Perceived teamwork; CO: Collaboration.

Table 4 shows that the Chi-square value (χ^2) is 1.75, with 1 degree of freedom (Γ), which is statistically significant at the 0.186 level; χ^2/Γ is 1.75; the NFI index is 1.00 and the CFI index is 1.00; lastly, the RMSEA is 0.02. These goodness-of-fit statistics show that the final path model fits very well with the data. Of the four statistically significant predictors of teamwork, safety culture (β =0.42) exerts the most influence on the variability in teamwork. Effective communication, job satisfaction and work climate have a positive influence on teamwork. For intra-organizational collaboration, work climate exerts (β = 0.88) more than three times the positive influence on collaboration than on team work. However, a negative and weak relationship of collaboration to effective communication and safety culture was found and reported in Table 4.

DISCUSSION

A relatively parsimonious path model was presented and evaluated. The findings reveal that a significant amount of variance in perceived teamwork (R^2 = 0.59) and in collaboration (R^2 = 0.75) is accounted for by the predictor variables. The most important predictor of perceived teamwork is safety culture, with a β weight of 0.42. The most significant predictor of collaboration is work climate, with a β weight of 0.85. Therefore, it is recommended that health care executives who are interested in improving collaboration should assess the work climate to ensure that employees are operating in a setting conducive to intra-organizational collaboration and cooperation. Considering previous research, a bizarre and surprising finding is that effective communication (β = -0.13) and safety culture (-0.08) are negatively associated with collaboration. It is believed that the measurement of effective communication should be revised to use quality indicators of communication that more accurately reflect how teamwork is facilitated by a favorable work climate.

Because the analysis is based on perceptions of employees in a single large medical center, its generalizability may be limited. It is unknown whether data drawn from

another sample would produce similar results. Future researchers could consider sampling employees from other comparable facilities and other industries to determine whether the findings could extend beyond the medical care organization sampled in this research. A related limitation is that the sample was disproportionately female; future researchers should sample males and females more evenly. Furthermore, including contextual and organizational characteristics for a variety of health care organizations could enhance the explanatory power of the predictor variables for teamwork and collaboration. Future research should therefore consider multilevel modeling of both work-unit and hospital characteristics that might be significant in determining the variability in teamwork and collaboration[22,23].

In conclusion, organizational behavior research needs to choose a proper theoretical framework for specifying the causal paths for validation. Without a proper theoretical framework, the creation of a path analysis model may be fruitless or groundless. Even with a well fitting model, using path analysis models without a theoretical framework is like shooting in the dark. It is the theoretical framework that must guide the researcher in assuming specific causal paths among the study variables.

It is clear that work climate has a large direct effect on intra-organizational collaboration. Safety culture has a moderate impact on teamwork. All of the other variables have a somewhat diminishing role in affecting the two endogenous variables, teamwork and collaboration. Taken together, the revised path analysis model explains a good proportion of the variance in both teamwork and collaboration. This new-found knowledge should be used to foster effective management of employees' safety culture and work climate. Mechanisms that either facilitate or impede effective teamwork should be explored and experimented with, as suggested by the expert panel from the Canadian Health Services Research Foundation[24] and other investigators[25-27]. Furthermore, improvement in work climate alone could substantially influence intra-organizational collaboration.

COMMENTS

Background

Safety culture is essential to the health care delivery system, particularly in a large medical center. The mechanisms for fostering work climate and safety environment are not well understood. Path analysis is an analytic tool to tease out complex causal relationships among many organizational variables that may directly and indirectly affect team work and collaboration within a large hospital.

Research frontiers

Organizational behavior research needs to choose a proper theoretical framework for specifying the causal paths for empirical validation. Path analysis enables to identify important mechanisms influencing team work and intra-organizational collaboration. Thus, patient safety measures could be properly institutionalized under an optimal work climate that stresses team work and collaboration.

Innovations and breakthroughs

The new-found knowledge about a strong and positive relationship of work climate to teamwork and collaboration in the hospital environment should be used to foster effective management of employees' perceptions of work environment and safety culture. Mechanisms that either facilitate or impede effective teamwork should be explored and experimented by health care executives.

Applications

Effective teamwork and collaboration have led the national recognition of exceptional quality of care delivered by the study hospital. This study has shed important light about the benefits of strengthening teamwork and collaboration within a complex organization. Other facilities could adopt similar organizational strategies in implementing mechanisms that could foster a productive environment.

Terminology

Intra-organizational collaboration: Patient safety is based collaborative efforts among health professionals, an essential component of delivering high quality of hospital care. This commonly shared mission by hospital employees has guided the development and implementation of many collaborative safety related programs.

Peer review

A limited number of intra-organizational studies on safety culture and work climate were found. This study offers new insight about factors influencing the variation in teamwork and intra-organizational collaboration in a very large medical facility. The results could be generalized to other large hospitals. Path analysis appears to be a parsimonious statistical tool to identify the relative importance of predictor variables in explaining the variability in teamwork and collaboration.

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Events Calendar 2012

January 20-21, 2012
AGA Clinical Congress of Gastroenterology and Hepatology: Practice, Evidence and Quality in 2012
Miami, FL, United States

January 26, 2012
Symposium of the Swiss Society of Pharmacology and Toxicology, Advances in Pharmacology - Cardiovascular Pharmacology
Bern, Switzerland

January 28 – February 1, 2012
LabAutomation2012
Palm Springs Convention Center, Palm Springs, CA, United States

February 1-4, 2012
3rd International Workshop on Medical Image Analysis and Description for Diagnosis System
Hotel Tivoli Victoria, Algarve, Portugal

February 24, 2012
State Stem Cell Agency Governance Subcommittee
San Francisco, CA, United States

March 11-14, 2012
Thoracic Imaging 2012
Hyatt Regency, Huntington Beach Resort and Spa, Huntington Beach, CA, United States

March 25-30, 2012
44th International Diagnostic Course Davos (IDKD)
Davos, Switzerland

April 26-29, 2012
75th Anniversary of the Canadian Association of Radiologists Annual Scientific Meeting
Le Centre Sheraton, Montreal, Quebec, Canada

April 29 - May 4, 2012
EUCHEM Conference on Stereochemistry
Brunnen, Switzerland

May 4-6, 2012
World Congress on Biotechnology
Hyderabad, India

June 7-9, 2012
ASCI 2012 - 6th Congress of Asian Society of Cardiovascular Imaging
Bangkok, Thailand

June 9-13, 2012
2012 Annual Meeting of the Society of Nuclear Medicine
Miami Beach, FL, United States

August 15-19, 2012
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October 28-30, 2012
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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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BRIEF ARTICLE

Use of the varying coefficient model in an exercise and depression meta-analysis

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Abstract

AIM: Use a recently developed varying coefficient model to determine the effects of exercise in adults with depression.

METHODS: Data from a recent meta-analysis addressing the effects of exercise on depression in adults were used. Studies were limited to randomized controlled intervention trials of any type of chronic exercise (for example, walking and jogging) in adults greater than or equal to 18 years of age with a diagnosis of depression. For each study, the standardized mean difference (exercise minus control) effect size for depression, adjusted for small-sample bias, was calculated. Variance statistics for each effect size and pooling of results were calculated using the recently proposed varying coefficient (VC) model for standardized mean differences. Standardized effect-sizes of 0.20, 0.50 and 0.80 were considered to represent small, medium and large effects. Results were considered statistically significant if the 95% confidence intervals did not cross 0, with negative results indicative of reductions in depression. These findings were then compared with results using traditional random-effects (RE) models.

RESULTS: A total of 23 studies representing 907 men and women (476 exercise, 431 control) were pooled for analysis. Both RE and VC models resulted in large, statistically significant improvements in depression as a result of exercise in adults. However, the VC model resulted in a larger overall effect size as well as confidence intervals that were narrower than previously reported using the RE model. The overall mean effect size for the RE model was -0.82 with a 95% confidence interval of -1.12 to -0.51. For the VC model, overall mean effect size was -0.88 with a 95% confidence interval of -1.08 to -0.68. The relative difference between the RE and VC approaches was 7.3%.

CONCLUSION: The VC model, a potentially preferable model, confirms the positive effects of exercise on depression in adults.

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Key words: Random-effects; Meta-analysis; Varying coefficient; Exercise; Depression

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INTRODUCTION

Depression is a major public health problem affecting an estimated 9.0% of adults in the United States[1]. A recent

meta-analysis using the traditional random-effects (RE) model reported statistically significant improvements in depressive symptoms as a result of any exercise modality in adults with depression[2]. However, since that time, a potentially more valid varying coefficient (VC) model has been proposed[3]. Given the importance of reaching accurate conclusions regarding a body of research, the objective of this brief report was to confirm the previously reported effects of exercise on depression in adults using the newly proposed VC model.

MATERIALS AND METHODS

Data source

Data from a recent meta-analysis addressing the effects of exercise on depression in adults, details of which have been described elsewhere, were used[2]. Briefly, studies were limited to randomized controlled intervention trials of any type of chronic exercise in adults ⩾ 18 years of age with a diagnosis of depression, as defined by trial authors[2].

Calculation and pooling of effect sizes for VC model

For each study, the standardized mean difference (exercise minus control) ES for depression, adjusted for small-sample bias, was calculated[4,5]. Variance statistics for each ES and pooling of results were calculated using the recently proposed VC model for standardized mean differences, a model that makes no assumptions with respect to a common ES or random sampling from a normally distributed super-population of studies[3]. The only assumption is that a random sample is obtained from each study population.

The mean unweighted estimate of the population standardized mean difference ES was calculated as follows:

$$\overline{\delta} = m^{-1}\sum_{i=1}^{m} b_i\hat{\delta}_i$$

where $\overline{\delta}$ is the pooled mean standardized ES, m represents each study, $\hat{\delta}$ is the standardized ES from each study, and b_i is Hedge's small sample-size adjustment for ESs, calculated as $b_i = 3/[4(/n_i + n_2)-9]$[5]. The independent samples variance for each study was calculated as:

$$\mathrm{var}(\hat{\delta}_i) = [\hat{\delta}_i^2(\hat{\sigma}_{i1}^4 / df_{i1} + \hat{\sigma}_{i2}^4 / df_{i2}) / 8\hat{\sigma}_i^4 + (\hat{\sigma}_{i1}^2 / df_{i1} + \hat{\sigma}_{i2}^2 / df_{i2})\hat{\sigma}_i^2]$$

where $df_{ij} = n_{ij}$ - 1 and $\hat{\sigma}_i = [(\hat{\sigma}_{i1}^2 + \hat{\sigma}_{i2}^2) / 2]^{1/2}$

The 95% confidence interval around the pooled standardized mean ES is calculated as:

$$\overline{\delta} \pm Z_{\alpha/2}[m^{-2}\sum_{i=1}^{m} b_i^2\,\mathrm{var}(\hat{\delta}_i)]^{1/2}$$

When compared to fixed-effect (FE) and RE approaches, the VC model has been shown to have superior coverage probabilities for standardized ESs[3]. Generally, standardized ESs of 0.20, 0.50 and 0.80 represent small, medium and large effects[6]. Results were considered statistically significant if the 95% confidence intervals did not cross 0, with negative results indicative of reductions in depression. All VC data were analyzed using Synthesizer 1.0[7].

RESULTS

A total of 23 studies representing 907 men and women (476 exercise, 431 control) were pooled for analysis[2]. Both RE and VC models resulted in large, statistically significant improvements in depression as a result of exercise in adults [RE, $\overline{\chi}$, 95% CI: -0.82 (-1.12 to -0.51); VC: -0.88 (-1.08 to -0.68)]. However, the VC model resulted in a larger overall ES of 7.3% as well as confidence intervals that were narrower than previously reported using the RE model[2].

DISCUSSION

Exercise, a nonpharmacologic intervention that can be implemented in the public health setting, has been reported to reduce depression in adults[2]. Using a recently developed and novel VC model[3], the findings of the current investigation support the overall results of a previous RE meta-analysis in which exercise resulted in improvements in depression among adults diagnosed with depression[2]. Confirmation of these findings is important given the prevalence and costs, estimated to be more than $83.1 billion in the year 2000, associated with depression in adults[1,8].

The two most common methods currently used to pool data in a meta-analysis are the FE model and the RE model. A FE model assumes that all studies share the same common ES and that any differences in effects are limited to sampling error. Consequently, study weights are limited to controlling for within-study error with no attention paid to between-study error. The FE model is usually appropriate if the studies included in the meta-analysis are identical and if the purpose is to calculate a common ES for the included studies and not generalize to other populations[9]. However, rarely are the studies included in a meta-analysis identical. In addition, one is usually interested in generalizing the findings to other populations. In contrast to the FE model, the RE model assumes that the true ES varies from study to study and they represent a random sample of true effects. Consequently, in a RE model, study weights are assigned to try and minimize both within and between-study variance[9]. Given the fact that RE models try to account for both within and between study variance, they are usually the preferred model to use. However, a major limitation of the RE model is the unrealistic assumption that each ES from the included studies is a random-sample of true effects. To try and address the problems associated with fixed and RE models, Bonett has recently proposed the VC model used in the current report[3]. As previously described, this model does not assume a common ES or random sampling of study populations and has been shown to have superior coverage probabilities to the fixed and RE models[3]. Importantly, simulation results suggest that confidence intervals based on the FE model are

too narrow while confidence intervals based on the RE model are too wide[3].

While the results for both RE and VC models in the current study were similar, the use of the VC model may be preferable given the greater coverage probabilities reported as well as the fact that the assumptions underlying the VC model may be more realistic in the meta-analytic setting[3]. For example, as previously mentioned, no assumptions with respect to a common ES or random sampling from a normally distributed population of studies are made with the VC model[3]. Thus, the larger ES and narrower confidence intervals from the VC model in this brief report may be a more accurate reflection of the effects of exercise in the treatment of depression among adults. Given the former, it is recommended that the VC model be considered when conducting meta-analytic research on depression and other mental health conditions. However, regardless of the model chosen, it's important to understand that the external validity of a meta-analysis depends not only on the statistical models used but also on the quality and representativeness of the individual studies included[7], factors not considered in this brief report. In conclusion, using the apparently more valid VC model, this brief report confirms the results of a previous RE meta-analysis with respect to exercise reducing depression in men and women diagnosed with depression[2].

COMMENTS

Background

Meta-analysis is a quantitative approach for synthesizing information from multiple studies and for reaching general conclusions regarding a body of research. The use of accurate statistical models for reaching such conclusions is important.

Research frontiers

A major area of current research with respect to meta-analytic methods is the development of more accurate methods for pooling results for meta-analysis. Currently, the random-effects (RE) model is the most preferred approach for pooling meta-analytic results. However, the RE model is based on the unrealistic assumption that results from the included studies are a random-sample of true effects.

Innovations and breakthroughs

Recently, the varying coefficient (VC) model has been proposed as an alternative model for meta-analysis. This model does not assume a common effect size or random sampling of study populations. It has been shown to perform better than both fixed and RE approaches. In this study, the authors compared the results of the VC model to the RE model using data from a meta-analysis on exercise and depression in adults, a major public health problem. While both models confirmed that exercise reduced depression in adults, the VC yielded a larger overall effect size and narrower confidence intervals.

Applications

The results of this study confirmed that exercise reduced depression in adults and that the VC may be preferred over the RE model.

Peer review

The results of the study confirm what it is already known with a new model for meta-analysis. The manuscript is well presented and easy to read. The title and the abstract reflect the topic and contents of the study. Methods are well presented and results provide sufficient experimental evidence to draw scientific conclusions.

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January 20-21, 2012
AGA Clinical Congress of Gastroenterology and Hepatology: Practice, Evidence and Quality in 2012
Miami, FL, United States

January 26, 2012
Symposium of the Swiss Society of Pharmacology and Toxicology, Advances in Pharmacology - Cardiovascular Pharmacology
Bern, Switzerland

January 28 – February 1, 2012
LabAutomation2012
Palm Springs Convention Center, Palm Springs, CA, United States

February 1-4, 2012
3rd International Workshop on Medical Image Analysis and Description for Diagnosis System
Hotel Tivoli Victoria, Algarve, Portugal

February 24, 2012
State Stem Cell Agency Governance Subcommittee
San Francisco, CA, United States

March 11-14, 2012
Thoracic Imaging 2012
Hyatt Regency, Huntington Beach Resort and Spa, Huntington Beach, CA, United States

March 25-30, 2012
44th International Diagnostic Course Davos (IDKD)
Davos, Switzerland

April 26-29, 2012
75th Anniversary of the Canadian Association of Radiologists Annual Scientific Meeting
Le Centre Sheraton, Montreal, Quebec, Canada

April 29 - May 4, 2012
EUCHEM Conference on Stereochemistry
Brunnen, Switzerland

May 4-6, 2012
World Congress on Biotechnology
Hyderabad, India

June 7-9, 2012
ASCI 2012 - 6th Congress of Asian Society of Cardiovascular Imaging
Bangkok, Thailand

June 9-13, 2012
2012 Annual Meeting of the Society of Nuclear Medicine
Miami Beach, FL, United States

August 15-19, 2012
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Daegu, South Korea

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The columns in the issues of *WJM* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide Guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in basic and clinical medical research methodology; (9) Brief Articles: To briefly report the novel and innovative findings in basic and clinical medical research methodology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJM*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of basic and clinical medical research methodology; (13) Guidelines: To introduce Consensuses and Guidelines reached by international and national academic authorities worldwide on the research basic and clinical medical research methodology; and (14) Voices: to publicize methodology-related communications that have been rejected or impossible for publication elsewhere due to evident prejudice and/or unreasonable reasons. Similarly, your experiences of the proven mistreatment during the past grant applications can be narrated or documented in this corner. The corresponding responses and echoes from readers are also welcome here.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

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Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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EDITORIAL

Statistical models for meta-analysis: A brief tutorial

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Abstract

Aggregate data meta-analysis is currently the most commonly used method for combining the results from different studies on the same outcome of interest. In this paper, we provide a brief introduction to meta-analysis, including a description of aggregate and individual participant data meta-analysis. We then focus the rest of the tutorial on aggregate data meta-analysis. We start by first describing the difference between fixed and random-effects meta-analysis, with particular attention devoted to the latter. This is followed by an example using the random-effects, method of moments approach and includes an intercept-only model as well as a model with one predictor. We then describe alternative random-effects approaches such as maximum likelihood, restricted maximum likelihood and profile likelihood as well as a non-parametric approach. A brief description of selected statistical programs available to conduct random-effects aggregate data meta-analysis, limited to those that allow both an intercept-only as well as at least one predictor in the model, is given. These descriptions include those found in an existing general statistics software package as well as one developed specifically for an aggregate data meta-analysis. Following this, some of the disadvantages of random-effects meta-analysis are described. We then describe recently proposed alternative models for conducting aggregate data meta-analysis, including the varying coefficient model. We conclude the paper with some recommendations and directions for future research. These recommendations include the continued use of the more commonly used random-effects models until newer models are more thoroughly tested as well as the timely integration of new and well-tested models into traditional as well as meta-analytic-specific software packages.

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INTRODUCTION

Meta-analysis is currently the most common approach for quantitatively combining the results of the same outcome from different studies. Indeed, the use of meta-analysis has increased dramatically over the past 30 years. For example, a recent PubMed search by the authors using the keyword "meta-analysis" resulted in 6 hits in the

year 1980 *vs* 6865 hits in the year 2010 (unpublished results). Meta-analysis can be accomplished using either an aggregate data (AD) or individual participant data (IPD) approach. Using an AD approach, summary data for the same outcome from each study, for example, change outcome means and standard deviations for resting systolic blood pressure, are pooled for statistical analysis. In contrast, an IPD meta-analysis includes the pooling of raw data for each participant from each included study. While the IPD approach might be considered the ideal in that it allows for such things as (1) standardizing statistical analyses from each study; (2) obtaining summary results directly, indigenous of study reporting; (3) checking the assumptions of models; (4) assessing participant-level effects; and (5) examining interactions[1], the obtainment of IPD as well as the associated costs for conducting an IPD meta-analysis can be prohibitive[1]. In addition, since the main interest in meta-analysis is often the overall result[2,3], both the IPD and AD approaches should yield similar findings[4,5]. Given these realities, the AD approach continues to be the most commonly used method for pooling the findings of separate studies. Congruent with the use of the AD approach is the need to select a model for combining findings from different studies as well as examining the potential influence of selected covariates on the overall results. Given the former, the purpose of this paper is to provide a brief tutorial of several models currently available for AD meta-analysis, with an emphasis on random-effects models.

FIXED *VS* RANDOM-EFFECTS META-ANALYSIS

The statistical aspects of an AD meta-analysis encompass a two-stage approach. In the first stage, the summary statistics from each study are calculated. In the second stage, these summary statistics from each study are combined to yield an overall result. The focus of this brief tutorial is on the second stage. For a more detailed description of stage one, the reader is referred to the work of Lipsey *et al*[6].

As previously mentioned, the meta-analyst is often most interested in the overall result(s)[2,3]. Borrowing from Harbord *et al*[7] and regardless of whether a fixed or random-effects model is used, conducting an AD meta-analysis requires that the analyst be able to derive from study i of n studies an estimate of the outcome of interest (γ_i) such as a difference in means or log odds ratio, and a standard error of the estimate σ_i, often which has to be estimated from other data in each study. A fixed-effect meta-analysis assumes that all observed variation is caused by the play of chance, that is, within-study sampling error. Thus, since all studies are assumed to measure the same overall effect, i.e., a single true effect size θ, the intercept-only fixed-effect model can be denoted as $\gamma_i = \theta + \varepsilon_i$ where ε_i represents the sampling error for γ_i.

In contrast, the intercept-only random-effects model allows θ_i to differ between studies under the assumption of a normal distribution around θ. This can be denoted as $\gamma_i = \theta + \varepsilon_i + \mu_i$, where μ_i represents the between study variance τ^2 that must be estimated from the data. Put more simply, a fixed-effect model tests the null hypothesis that there is zero effect in every study while a random-effects model tests the null hypothesis that the mean effect is zero[8]. The fixed-effect model is appropriate for an AD meta-analysis when all included studies are identical and the goal is to estimate a common effect size for the identified population and not generalize to the rest of the population. However, since most researchers are probably interested in generalizing results across a variety of situations and the included studies are unlikely to be functionally equal, the random-effects model is usually the more appropriate model[8,9].

In addition to generating an overall effect size from the pooling of studies, one may also be interested in looking at the effect of potential covariates on the overall effect size, especially, but not exclusively, when significant between-study heterogeneity exists. Since the random *vs* fixed-effect model is usually the more appropriate model to use, we focus our discussion on the random-effects model in the form of regression, i.e., meta-regression. This is denoted as $\gamma_i = x_i\beta + \mu_i + \varepsilon_i$, where the single linear covariate (predictor) $x_i\beta$ replaces the mean θ.

Several different types of random-effects meta-regression models have been recommended for use in an AD meta-analysis, the primary difference being in the calculation of the between-study variance τ^2[10]. These models may be better described as mixed-effects models when covariates are included. However, in order to avoid confusion, they will continue to be described as random-effects models.

Regardless of the model chosen, random-effects meta-regression models will initially estimate τ^2, the between-study variance, followed by β, the regression coefficients. The regression coefficients are calculated using weighted least squares, $1/(\sigma_i^2 + \tau^2)$, where σ_i^2 represents the standard error of the estimated effect size from study i.

Currently, the most common random-effects meta-regression model used is an extension of the noniterative method of moments approach originally proposed by DerSimonian *et al*[11]. For this model τ^2 is estimated as:[12]

$$\hat{\tau}^2 = \frac{Q_{res} - (n+k)}{\Sigma i\{1/\sigma_i^2(1-hi)}$$

where Q_{res} is the residual weighted sum of squares heterogeneity statistic, calculated as:

$$\sum_i \left(\frac{y_i - x_i\hat{\beta}}{\sigma_i}\right)^2$$

and h_i represents the ith diagonal element of the hat matrix $X(X'V_0^{-1}X)^{-1}XV_0^1$, and V_0 = diagonal $(\sigma_1^2, \sigma_2^2, \ldots \sigma_n^2)$.

Based on the work of Higgins *et al*[13], the proportion of residual heterogeneity is calculated as:

$$I^2 = \max\left\{\frac{Q_{res} - (n-k)}{Q_{res}}, 0\right\}$$

Table 1 Meta-regression models for changes in triglycerides (mg/dL)

Variable	Studies (*n*)	Participants (*n*)	β	σ	z	p(z)	95% CI	τ^2	I^2_{res}
Model 1 (intercept-only)									
Intercept	6	559	-9.4	3.7	-2.5	0.01	-16.6 to -2.1	65.4	98.8
Model 2 (intercept + 1 covariate)									
Intercept	6	559	7.5	5.9	1.3	.02	-4.1 to 19.1		
Bodyweight (kg)	6	559	2.9	0.9	3.2	.001	1.1 to 4.8	15.1	93.7

β: Coefficient; σ: Standard error; z: z-value; p(z): Alpha value for z; 95% CI: 95% confidence interval; τ^2: Tau-squared between-study variance; I^2_{res}: Percentage of residual heterogeneity that is attributable to between-study heterogeneity.

Adjusted R^2 (the proportion of between study variance explained by the covariates) is calculated as

$$R^2_Q = (\hat{\tau}^2_0 - \hat{\tau}^2) / \hat{\tau}^2_0$$

where $\hat{\tau}^2$ is the estimate of the between-study variance in the model with covariates and $\hat{\tau}^2_0$ is the estimate of the between-study variance without covariates, i.e., intercept-only model.

Summary random-effects estimates do not provide any information regarding how treatment effects from new individual trials are distributed around the summary effect[14]. This may be problematic since the treatment effect is assumed to vary between studies when a random-effects model is used. Recently, prediction intervals have been developed and recommended for determining how treatment effects from new individual trials are distributed about the mean in a random-effects meta- analysis[14]. This is calculated as

$$\hat{\mu} \pm t^a_k - 2\sqrt{\widehat{SE}(\hat{\mu})^2 + \hat{\tau}^2}$$

where $\hat{\mu}$ is the average weighted estimate across studies, t^a_k - 2 is the 100 (1 - α/2)% percentile of the t-distribution with k-2 degrees of freedom, $\widehat{SE}(\hat{\mu})^2$ is the estimated squared standard error of $\hat{\mu}$, and $\hat{\tau}^2$ is the estimated between study variance. This is in contrast to obtaining a confidence interval of $\hat{\mu} \pm 1.96\ \widehat{SE}(\hat{\mu})^2$ [14,15]. As previously described in more detail[15], the major point is that the variability between studies, as measured by $\hat{\tau}^2$, needs to be included when making predictions for a new study but not if making inferences about the average effect size. In addition, using the t-distribution *vs* the normal distribution for prediction intervals is in recognition of the fact that it is estimated rather than being known. Furthermore, it is important to understand that conclusions based on prediction intervals should not be used to determine whether confidence intervals for underlying mean effects are correct or incorrect since prediction intervals are based on a random mean effect while confidence intervals are not.

RANDOM-EFFECTS ANALYSIS (A BRIEF EXAMPLE)

Data from a previously published meta-analysis of six randomized controlled trials addressing the efficacy of combined aerobic exercise and diet on lipids and lipoproteins in adult men and women at least 18 years of age will serve as the brief example[16]. This dataset reflects the real world of AD meta-analysis with respect to the small number of studies that are usually included and while being mindful that participants are nested within studies, thereby increasing power and precision[17,18]. The focus of the example is on effect size changes in triglycerides, a continuous variable and one of the primary outcomes of the original meta-analysis[16]. At stage one, effect sizes from each study were calculated by subtracting the change score in the intervention group (aerobic exercise and diet) from the change score in the control group. Negative values were indicative of improvements (reductions) in triglycerides. Variances were calculated from the pooled standard deviations of change scores in the intervention and control groups. At stage two, results were pooled using method of moments random-effects meta-regression[11]. While somewhat arbitrary, residual heterogeneity (I^2_{res}) was classified as small (< 50%), medium (50% to < 75%) and large (≥ 75%)[19]. All data were analyzed using the updated metareg command (version 2.2.6)[7] in version 11.2 of Stata[20].

The intercept-only results are shown in Table 1, Model 1. As can be seen, a statistically significant decrease of approximately 9 mg/dL was observed for triglycerides as a result of a combined aerobic exercise and diet intervention. In addition, non-overlapping confidence intervals were found. However, based on fixed-effect analysis, there was a large amount of residual variation attributable to heterogeneity (I^2_{res}). This is not uncommon in meta-analysis. The 95% prediction interval for a new trial was -34.08 to 15.35 mg/dL. While a lack of substantial residual heterogeneity should not exclude one from conducting covariate analysis, the presence of a large amount of heterogeneity does provide support for such. Table 1, Model 2 includes effect size changes in bodyweight (change outcome difference between the intervention and control group) as a single covariate. As can be seen, body weight is a statistically significant covariate for triglycerides. For every 1 kg decrease in bodyweight, an approximate 3 mg/dL decrease in triglycerides can be expected. The adjusted R^2 is 76.9%, meaning that 76.9% of the between-study variance (93.7%) is explained by changes in bodyweight while the remaining 23.1% is unexplained. Importantly, the 76.9% and 23.1% sum to 100% because we're solely concerned here with the variance between

studies and not the within-study variability. Additionally, from the I^2_{res} output in Table 1, Model 2, a large amount of residual variation is still due to heterogeneity (93.7%) while only 6.3% is attributable to within-sample variability. Thus, while decreases in bodyweight appear to be a strong predictor of decreases in triglycerides, a large amount of between-study heterogeneity continues to exist. This suggests that other covariates are also contributing to between-study heterogeneity. This occurrence is not uncommon in meta-analysis[13]. To address this issue, a radically different approach has recently been proposed in which a formal process for soliciting opinions is sought from quantitatively trained assessors regarding internal biases and subject-matter specialists regarding external biases[21,22]. After adjusting for these biases, the authors reported no apparent heterogeneity[21].

DISCUSSION

Irrespective of the type of meta-regression model chosen, it's important to realize that when conducting a meta-analysis, studies are not randomly assigned to covariates[23]. Consequently, meta-regression that includes covariates is considered to be observational in nature and thus, does not support causal inferences. Rather, the validity of these findings would need to be tested in large, well-designed randomized controlled trials.

While the original DerSimonian and Laird random-effects model is the most widely used[11], it may not be the most appropriate. For example, Brockwell *et al*[24] found that even with large sample sizes, the intervals based on the DerSimonian and Laird method did not attain the preferred coverage for the odds-ratio. This appeared to be the result of the estimated inverse variance weights that included estimates of the variance component. The DerSimonian and Laird approach has also been critiqued by Hardy *et al*[25]. While not commonly used, DerSimonian *et al*[26] have recently provided updated random-effects models that they believe are more valid than the original DerSimonian and Laird model. These models include two new two-step methods that appear to approximate the optimal iterative method better than the earlier and most commonly used one-step non-iterative method[11].

Alternative and more computationally intensive parametric random-effects models for estimating between-study heterogeneity in an AD meta-analysis have been proposed. These include, but are not necessarily limited to, maximum likelihood, restricted maximum likelihood and profile likelihood[10,25,27]. One nonparametric random-effects model, the permutations model, has also been proposed for estimating the between-study variance in an aggregate data meta-analysis[28]. While not discussed further, the empirical Bayes model for estimating τ^2 has also been proposed for random-effects meta-analyses[27]. However, the results for such have been mixed[10,29].

As described by others[30], the maximum likelihood model assumes that both the within and between-study effects have normal distributions. The between-studies variance for the log-likelihood function is then solved iteratively. Unfortunately, this model does not always converge, the end result being that estimates are reported as missing. In addition, when the between studies variance is negative, it is set to zero. When this occurs, the model collapses into a fixed-effect model.

Coterminous with the maximum likelihood approach, the restricted maximum likelihood model also follows the same assumptions of normal within and between-study effects. However, unlike the maximum likelihood model, only that portion of the likelihood function that doesn't change, for example, μ if estimating τ^2 is maximized. Another similarity to the maximum likelihood approach is that this method doesn't always converge, resulting in estimates being reported as missing. In addition, when the between-studies variance is negative, the model collapses into a fixed-effect model.

Thompson *et al*[10] advocate for the use of a restricted maximum likelihood model but not the maximum likelihood model because the latter does not account for the degrees of freedom employed when estimating the fixed-effect portion of the model. The end result is a smaller $\hat{\tau}^2$ and standard errors. This may be particularly relevant when the number of studies included is small, a common occurrence in meta-analysis.

The profile likelihood method also utilizes the same function as the maximum likelihood model. However, unlike the maximum likelihood model, nested iterations that converge to a maximum are used to account for the uncertainty associated with the between studies variance. However, similar to the maximum likelihood and restricted maximum likelihood models, the model doesn't always converge. Consequently, values not calculated are reported as missing. In addition, the confidence intervals produced by this model are asymmetric.

A nonparametric random-effects approach for estimating between-study heterogeneity is the permutations model described by Follmann *et al*[28]. By permuting the sign of each observed effect, a dataset of observed study outcomes is generated under the assumption that all true study effects are zero and observed effects are due to random variation. The original DerSimonian and Laird model[11] is then used to estimate an overall effect size for each combination. Based on the distribution of these effect sizes, asymmetric confidence intervals as well as heterogeneity statistics are estimated.

When conducting an AD meta-analysis, one is usually interested in a fast, efficient and accurate way of not only calculating the outcome of interest (intercept-only model) but also the association with one or more predictor variables with the outcome of interest (meta-regression). With the former in mind, the user-written routine metaan[30], developed for use in the general statistics package Stata[20], allows one to conduct random-effects AD meta-analysis using the method of moments, maximum likelihood, restricted maximum likelihood and profile likelihood approaches. In addition, the metareg user-

written routine[7], also for Stata[20], allows one to calculate the method of moments, maximum likelihood, restricted maximum likelihood and empirical Baye's estimate. Comprehensive meta-analysis[31], a statistical software package developed specifically for AD meta-analysis, allows the user to conduct random-effects analysis using the method of moments and maximum likelihood approaches. However, only a single predictor (simple meta-regression) is allowed in each model.

While random-effects models are generally preferred over fixed-effect models, random-effects models also have disadvantages. For example, random effects models assume that study-level effect sizes are sampled from a larger distribution of effect sizes[8]. However, this may not be realistic. In addition, the smaller the number of studies included, the poorer the estimate of $\hat{\tau}^2$, i.e., weaker precision[8]. Unfortunately, to the best of the authors' knowledge, no definitive cutpoint for what constitutes a small number of studies has been established.

Alternative models to both fixed and random-effects meta-analysis for aggregate data have recently been proposed. For example, Bonett *et al*[32-34] has advocated for what is known as the varying coefficient model. As described by Krizan *et al*[35], Bonett argues that current fixed-effect models inappropriately assume a common effect size across all included studies and perform poorly when heterogeneity exists while current random-effects models require unrealistic assumptions about random sampling of observed effect sizes from a normally distributed "superpopulation". In contrast, the varying coefficient model makes no assumptions with respect to a common effect size or random sampling of study populations from a normally distributed, well-defined "superpopulation" of studies. The varying coefficient model has been shown to have better coverage probabilities than both fixed and selected random-effects models when applied across a variety of statistics[32-34], including unstandardized and standardized mean differences[32]. Other alternative models have also been recently proposed by Kulinskaya *et al*[36].

In time, it is likely that the DerSimonian *et al*[11] approach will be replaced by more accurate and precise models. However, at this time, it is probably imprudent to over-react to newly proposed models. This is especially true since many of the alternatives proposed as a means of dealing with specific problems in meta-analysis may turn out to have problems of their own, often with substantially worse impact than the problems they were intended to solve. In addition, the usually minor differences in results from the use of different random-effects approaches for meta-analysis may have little effect on the "big picture", something that should be considered as practically relevant. The former notwithstanding, a need exists for extensive testing of all current models as well as the development of newer ones across a variety of different scenarios. In addition, a gap exists between the development and testing of these models and their timely integration into traditional as well as meta-analytic-specific software packages, one or both of which are probably used by the vast majority of those conducting meta-analytic research. However, from our perspective, the final decision about when a model is ready for widespread use is truly Solomonic.

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January 20-21, 2012
AGA Clinical Congress of Gastroenterology and Hepatology: Practice, Evidence and Quality in 2012
Miami, FL, United States

January 26, 2012
Symposium of the Swiss Society of Pharmacology and Toxicology, Advances in Pharmacology - Cardiovascular Pharmacology
Bern, Switzerland

January 28 – February 1, 2012
LabAutomation2012
Palm Springs Convention Center, Palm Springs, CA, United States

February 1-4, 2012
3rd International Workshop on Medical Image Analysis and Description for Diagnosis System
Hotel Tivoli Victoria, Algarve, Portugal

February 24, 2012
State Stem Cell Agency Governance Subcommittee
San Francisco, CA, United States

March 11-14, 2012
Thoracic Imaging 2012
Hyatt Regency, Huntington Beach Resort and Spa, Huntington Beach, CA, United States

March 25-30, 2012
44th International Diagnostic Course Davos (IDKD)
Davos, Switzerland

April 26-29, 2012
75th Anniversary of the Canadian Association of Radiologists Annual Scientific Meeting
Le Centre Sheraton, Montreal, Quebec, Canada

April 29 - May 4, 2012
EUCHEM Conference on Stereochemistry
Brunnen, Switzerland

May 4-6, 2012
World Congress on Biotechnology
Hyderabad, India

June 7-9, 2012
ASCI 2012 - 6th Congress of Asian Society of Cardiovascular Imaging
Bangkok, Thailand

June 9-13, 2012
2012 Annual Meeting of the Society of Nuclear Medicine
Miami Beach, FL, United States

August 15-19, 2012
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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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ORIGINAL ARTICLE

LC-MS/MS analysis of 2-aminothiazoline-4-carboxylic acid as a forensic biomarker for cyanide poisoning

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Abstract

AIM: To demonstrate the potential of using 2-aminothiazoline-4-carboxylic acid (ATCA) as a novel biomarker/forensic biomarker for cyanide poisoning.

METHODS: A sensitive method was developed and employed for the identification and quantification of ATCA in biological samples, where the sample extraction and clean up were achieved by solid phase extraction (SPE). After optimization of SPE procedures, ATCA was analyzed by high performance liquid chromatography-tandem mass spectrometry. ATCA levels following the administration of different doses of potassium cyanide (KCN) to mice were measured and compared to endogenous ATCA levels in order to study the significance of using ATCA as a biomarker for cyanide poisoning.

RESULTS: A custom made analytical method was established for a new (mice) model when animals were exposed to increasing KCN doses. The application of this method provided important new information on ATCA as a potential cyanide biomarker. ATCA concentration in mice plasma samples were increased from 189 ± 28 ng/mL (n = 3) to 413 ± 66 ng/mL (n = 3) following a 10 mg/kg body weight dose of KCN introduced subcutaneously. The sensitivity of this analytical method proved to be a tool for measuring endogenous level of ATCA in mice organs as follows: 1.2 ± 0.1 μg/g for kidney samples, 1.6 ± 0.1 μg/g for brain samples, 1.8 ± 0.2 μg/g for lung samples, 2.9 ± 0.1 μg/g for heart samples, and 3.6 ± 0.9 μg/g for liver samples.

CONCLUSION: This finding suggests that ATCA has the potential to serve as a plasma biomarker / forensic biomarker for cyanide poisoning.

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Key words: Forensic science; Biomarker; Cyanide poisoning; 2-aminothiazoline-4-carboxylic acid; LC-MS/MS

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INTRODUCTION

Cyanide is a swift and powerful poison. Suicidal, accidental, or homicidal death involving the determination of cyanide is encountered frequently in forensic toxicological practice[1]. In crime scene investigations, two indicators of acute cyanide poisoning are (1) a "bitter almond" odor emanating from the victim; and (2) the presence of pink lividity in the post mortem examination[2]. The presence of cyanide can be confirmed chemically using a colorimetric test at the scene of the crime, followed by a laboratory analysis using a gas chromatography-mass spectrometry (GC-MS). Samples, such as stomach contents and whole blood are usually collected from victims and analyzed in order to confirm the cause of death[3]. The determination of the presence of cyanide involves extraction of hydrogen cyanide (HCN) from samples and the measurement of cyanide from the extracts[4,5]. Biological fluids, such as blood or urine can be taken from the subject for analysis[6-9]. Due to the relatively short half-life of cyanide (from minutes to hours depending on the matrix), direct analysis of cyanide to confirm cyanide poisoning may only be feasible within the first few hours following exposure[10-12].

Natural dietary and pulmonary intake of cyanide from the environment provides a nonzero cyanide background level in the body. Smoke inhalation in fires greatly increases background cyanide levels[13]. The volatility and reactivity of cyanide leaves direct measurements highly susceptible to errors introduced during the sample collection and separation step[14]. An alternative approach that can help to minimize false positive (no cyanide is involved but cyanide is detected) and false negative (cyanide is involved but cyanide is not detected) results, is to detect stable biomarkers of cyanide, rather than cyanide itself. Thiocyanate (SCN^-), 2-aminothiazoline-4-carboxylic acid (ATCA), and cyanide-protein adducts in biological fluids and tissues have been reported as alternative biomarkers for cyanide exposure and poisoning[15,16]. SCN^- is the major cyanide metabolite found in blood[17]. However, SCN^- is also a natural metabolite of non-cyanide mediated pathways and thus is not a good marker for cyanide exposure[18].

Detoxification of cyanide by cystine to produce ATCA *in vivo* was first reported by Wood and Cooley[19]. They found that the pathway producing ATCA represents approximately 20% of cyanide metabolism, that the quantity of ATCA produced is directly proportional to the amount of cyanide metabolized, and that harvested ATCA is stable for months in the freezer[20]. Therefore, ATCA has been considered a promising candidate as a chemically stable biomarker for cyanide poisoning. More details of human metabolism of cyanide and detection of its biomarkers can be found in a recent review published by Logue *et al*[21]. Aside from the -cyanide mediated pathway, there are currently no other known pathway for endogenous ATCA production in the human body.

There are numerous analytical techniques to determine cyanide[22] and thiocyanate[23] or both[24,25] in biological samples, but only a few techniques are available to measure ATCA. Quantitative analysis of ATCA begins with extraction from biological samples followed by derivatization to produce a sample that is suitable for quantitative analysis with liquid chromatography or gas chromatography. Cation exchange solid-phase extraction (SPE) columns and individual pre-treatment steps for the extraction and analysis of ATCA from biological samples have been reported[26,27]. Derivatization steps were needed in those studies due to the use of either fluorometric detection or gas chromatography. Molecularly imprinted stir bar sorption extraction (MISBSE) of ATCA was reported by Jackson *et al*[28]. The MISBSE technique enables the selective extraction of ATCA from urine samples followed by direct detection of ATCA (without derivatization) by a tandem mass spectrometer. This technique may in the future provide rapid analytical method for the direct detection of ATCA for forensic urine analysis, but at the moment, MISBSE is not competitive with standard SPE methods due to the low binding capacities and sample recoveries.

The purpose of this study was to determine the optimal conditions for the quantification of ATCA in various biological fluids and organs using SPE, and high performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Conditions associated with SPE sample loading, washing and final elution, were studied and refined. The effect of ATCA signal fluctuations arising from electrospray ionization (ESI) suppression was minimized by using a structural analogue of ATCA (2-aminothiazole-4-carboxylic acid, ATZA) as an internal standard. Similar LC-MS/MS analysis was previously reported and employed for different purposes with different experimental setups on different animal (rat) models[29,30]: Determining ATCA levels in plasma and various organs after a constant dose of cyanide exposure [4 mg/kg potassium cyanide (KCN)] indicated that the plasma ATCA level following cyanide exposure was not significantly elevated from the endogenous ATCA level. This suggested that ATCA might not be a good biomarker for cyanide intoxication[29]; however, this study also demonstrated that ATCA is a valuable forensic biomarker, since the ATCA level significantly increased in certain organs after a constant dose (4 mg/kg) of KCN administration. To determine how long ATCA persists in the circulation, ATCA was injected to the bloodstream, and samples were taken at periodic time intervals, and analyzed by the LC-MS/MS method[30]. Results suggested that ATCA is a chemically stable metabolite, suitable as a forensic biomarker. This study also compared the two sample preparation methods of SPE and MISBSE suggesting the priority of SPE over MISBSE. Present studies are reporting ATCA levels after exposing mice to higher, increasing (6, 6, 8 and 10 mg/kg) KCN doses. Exogenously elevated levels of ATCA were compared to endogenous levels of ATCA present in the biological fluids and organs prior to challenge. This new method can be extended to future toxicokinetic studies of ATCA in other animal models in order to confirm the significance of using ATCA as a

biomarker from different biological matrices for human cyanide poisoning.

MATERIALS AND METHODS

Ethics

All animal procedures were conducted in accordance with the guidelines in The Guide for the Care and Use of Laboratory Animals (National Academic Press, 1996). The research facility was accredited by AAALAC (American Association for the Assessment and Accreditation of Laboratory Animal Care, International) and this animal study was approved by the IACUC (Institutional Animal Care and Use Committee) at Sam Houston State University.

Chemicals and samples

Trifluoroacetic acid (TFA) was obtained from EMD Chemicals (Gibbstown, NJ, USA) and used to prepare 0.5% (v/v) TFA in methanol (0.5% TFA/MeOH) as the mobile phase. All solvents were at least HPLC grade. ATCA was obtained from Chem-Impex International (Wood Dale, IL, USA). ATZA was obtained from Synthonix (Wake Forest, NC, USA). Molecular structures of ATCA and ATZA are shown in Figure 1. KCN was purchased from Sigma-Aldrich (St. Louis, MO, USA). For *in vivo* study, serial dilutions were used to produce aqueous KCN solutions of systematically decreasing concentration. KCN is acutely toxic. Ingestion of KCN or exposure to its salt or its aqueous solutions by eye or skin contact can be fatal. Exposure to as little as 50-150 mg can cause immediate collapse and death. Working with cyanide-containing compounds requires special care. Oasis® mixed mode cation exchange (MCX) cartridges were obtained from Waters Corporation (Milford, MA, USA). A 5% aqueous ammonium hydroxide/methanol solution (v/v) was prepared and used as the final elution solution. Mice liver, plasma, brain, heart and lung were used to evaluate the applicability of the analytical method.

Instrumentation

SPE was performed in a glass manifold equipped with Teflon needle inserts and evacuated with a Buchi V-700 Vacuum Pump (Mallinckrodt Baker, Inc., Phillipsburg, NJ, USA). Homogenization was performed with ready-to-use Precellys® lysing kits on a Precellys-24 tissue homogenizer (Bertin Technologies, France). Pierce Reacti-Therm II Heating Module was used to stream air to borosilicate glass disposable culture tubes (13 mm × 100 mm). A Shimadzu liquid chromatograph (LC-20AT, Shimadzu, Columbia, MD) coupled to a tandem mass spectrometer (API 3200 ESI/MS/MS system, Applied Biosystems, Foster City, CA) was employed for the LC-MS/MS separation, detection and quantification of ATCA. A Luna CN column (3 micron, 100 mm × 2 mm; Phenomenx; Torrance, CA, USA) was used for the separation. A 5 μL aliquot was injected to the LC-MS/MS by an auto-sampler, and eluted isocratically at a 0.5 mL/min flow rate. Transition ions of ATCA in positive mode (m/z 147 → 101) and ATZA (m/z 145 → 127) were generated using ESI and detected using multiple reaction monitoring (MRM). The source dependent conditions of ESI were as follows: ionspray voltage: +5500 V, temperature: 450 ℃, curtain gas 350 kPa, gas 1: 480 kPa, gas 2: 140 kPa. The compound dependent parameters were as follows: collision gas (CAD): 41 kPa, collision cell entrance potential: 14 V, and the collision cell exit potential: 4 V. More instrumentation details of ESI/MS/MS for the detection of ATCA can be found in our previous report[24].

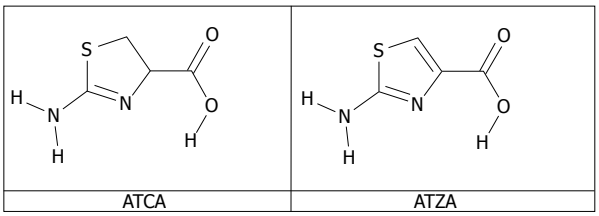


Figure 1 Molecular structures of 2-aminothiazoline-4-carboxylic acid and 2-aminothiazole-4-carboxylic acid. 2-aminothiazole-4-carboxylic acid (ATZA) served as an internal standard. ATCA: 2-aminothiazoline-4-carboxylic acid.

Sample preparation and SPE procedure

ATCA standard solutions with concentrations ranging from 0-1000 ng/mL, were prepared from 330 μg/mL ATCA standard stock solutions by serial dilutions. Internal standard, 10 μg/mL of ATZA, was prepared from a 282 μg/mL ATZA standard stock solution. Both ATCA and ATZA stock solutions were prepared in mobile phase (0.5% TFA/MeOH). To construct the calibration curve, 200 μL of each standard solution was mixed with 20 μL of internal standard. The standard solutions were sonicated for 5 min and then dried. They were reconstituted with 220 μL of mobile phase, and then a 5 μL aliquot was injected to the LC-MS/MS for analysis.

To prepare the ATCA spiked samples, known amounts of ATCA were air-dried in the test tubes. Two hundred microliters of sample (urine, plasma, and organ homogenates) and 20 μL internal standard were added to these test tubes and diluted with 800 μL of 10 mmol/L phosphate buffer (pH 7.4) before SPE. For organ homogenization, samples were thawed, chopped, and weighed in homogenizing tubes, and 0.1 mol/L HCl was added to make a concentration of 0.6 g organ mass/mL in each tube. The samples were homogenized for 3 min, 1 min per cycle with 3 cycles at 6000 r/min using the Precellys 24. Homogenized mixtures of samples were diluted with 10 mmol/L phosphate buffer (pH 7.4) to obtain a final concentration of organ homogenate of 0.15 g organ mass/mL buffer. The solution was vortexed and centrifuged for 10 min at 10 000 r/min and the supernatant was removed for the SPE extraction.

SPE was performed on a MCX cartridge prior to the LC-MS/MS analysis. The MCX cartridges were conditioned with 1 mL of methanol and then 1 mL of distilled water. The samples (1 mL total) were loaded into the conditioned

cartridges employing vacuum as needed. After sample loading, the cartridges were washed with 1 mL of 0.1 mol/L HCl first and then washed with 1 mL methanol. The cartridges were finally eluted with 1 mL of 5% (v/v) ammonium hydroxide in methanol (5% NH_4OH/MeOH). Note that teflon inserts and waste test tubes were replaced with clean inserts and glass test tubes before final elution. The eluates were air dried first, then reconstituted with 220 μL of mobile phase. After sonication for 5 min, the reconstituted samples were transferred to LC-MS/MS auto-sampler vials containing 250 μL glass inserts.

Quantitative analysis of ATCA

Detection of ATCA by ESI/MS/MS has been previously reported[24]. Briefly, 5 μg/mL ATCA and ATZA standard solutions were infused separately to the MS/MS at 10 μL/min in order to observe certain compound-dependent parameters for MRM transitions. When ATCA standard solution was infused to the ESI source under optimal ESI conditions, the ATCA molecular ion at m/z 147, corresponding to $(M + H)^+$, was detected. ATCA product ion at m/z 101 was the most abundant product ion after the optimization of compound-dependent parameters of MRM, hence the transition ion m/z 147 → 101 was selected for identification and quantification of ATCA. Similarly, ATZA molecular ion at m/z 145 was generated under the optimal ESI condition. Its product ion m/z 127 was the most abundant product ions after optimization of compound-dependent parameters of MRM, hence the transition ion m/z 145 → 127 was selected for detection of the internal standard (ATZA). An internal standard corrected calibration curve was constructed by plotting the ratio of ATCA peak area to ATZA peak area *vs* ATCA concentrations. External calibration curves were also constructed to examine matrix and ionization suppression effects.

Quality control

The quality control (QC) sample was a 200 μL, 500 ng/mL ATCA standard with 20 μL of 10 μg/mL internal standard. The QC was analyzed prior to each sample to ensure that the instrumentation was working properly. Additionally, a blank sample (mobile phase with the internal standard only) was also run between samples to check for any potential carryovers. The peak shape for the QC was confirmed first, and any deviation from the known peak shape was interpreted as an instrumentation error. Conditioning of separation column and tubing was performed when high backpressure was noticed. Once QC was passed, samples were analyzed using LC-MS/MS with good confidence.

Animal studies

For animal studies, Charles River provided the 18 CD-1 mice, all of which were male and weighed about 20 g. The experimental animals were housed in room temperature and light controlled rooms (22 ℃ ± 2 ℃, 12-h light/dark cycle). They were furnished with water and Teklad Rodent Diet (W) 8604 (Teklad HSD, Inc., WI, USA) ad libitum. Plasma and organs (brain, lungs, heart, liver, and kidneys) of the mice were collected after subcutaneous injection of KCN at different doses. Three sublethal doses (6, 8, and 10 mg/kg-body-weight) were applied (3 mice/dose), and the injection solutions were prepared from a 4-mg/mL KCN stock solution. Each dose was injected with a 25 G × 1 1/2 needle. Mice were terminated 15 min after cyanide exposure and organs were collected. Blood samples were taken by pipetting. The average volume of blood obtained was 0.25 mL, and the blood was placed into Eppendorf tubes with 40 L of 10 mg/mL of heparin in water. The Eppendorf tubes were vortexed, then centrifuged at 13 000 r/min for 5 min. Plasma was collected, and organs were collected as well. Plasma and organ samples were placed into plastic 3 mL tubes and stored in the freezer until they were thawed for analysis. Note that longer exposure of cyanide was not performed in this work. The toxicokinetic and half-life studies of ATCA are separate research projects in our laboratory.

RESULTS

SPE procedure

The use of MCX cartridge for the extraction of ATCA from acidified urine samples has been previously reported[20]. The ACTA was eluted from the cartridge by concentrated NH_4OH and converted to the trimethylsilyl derivative through reaction with 30% N-methyl-N-trimethylsilyltrifluoroacetamide (MSTFA) in hexane before analysis by GC-MS. In our work, we have modified and optimized the SPE procedure for LC-MS/MS instrumentation. ATCA was detected by ESI-MS/MS without chemical derivatization. The impact of solvent composition on ATCA and ATZA ionization at the ESI source was tested first. Solvents of three ATCA standard solutions (500 ng/mL with ATZA) were evaporated by air (air-dry) and argon (argon-dry) gases and the residues were reconstituted with a freshly prepared mobile phase. As shown in Figure 2, the MS/MS signals of ATCA and ATZA were compared with and without air drying. The decreased peak areas of ATCA and ATZA in reconstituted solutions following air or argon drying were attributed to the variations of TFA concentration in the stock solution and the freshly prepared mobile phase. Solvent evaporation with argon had similar effects to that with air. Therefore, the use of an inert gas was not needed for solvent evaporation. It has been known that TFA is a good organic additive in chromatography, but a poor reagent for MS/MS signal. In our method development, it was unfortunate that we could not avoid the need for evaporation of samples and calibration standards.

Concentrated (28%-30%) aqueous ammonium hydroxide, 5% NH_4OH/MeOH, 0.5% TFA/MeOH, and 1% TFA/MeOH were next tested to determine the optimal final elution solution. Triplicates of each solution were performed through SPE. The optimal final elution solution was also determined by using 2 different elution

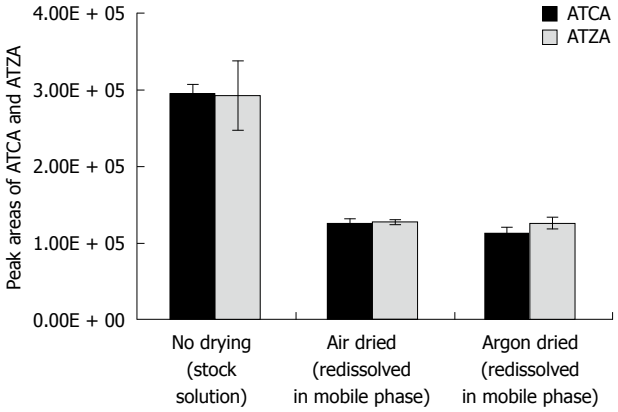


Figure 2 Comparison of 2-aminothiazoline-4-carboxylic acid and 2-aminothiazole-4-carboxylic acid signals detected by LC-MS/MS before and after evaporation of solvents by air or argon stream. The decreased peak areas of 2-aminothiazoline-4-carboxylic acid (ATCA) and 2-aminothiazole-4-carboxylic acid (ATZA) in reconstituted solutions following air or argon drying were attributed to the variations of trifluoroacetic acid concentration in the stock solution and the freshly prepared mobile phase. Solvent evaporation with argon had similar effects to that with air. Therefore, the use of an inert gas was not needed for solvent evaporation.

volumes (1 and 2 mL) of 5% NH_4OH/MeOH. Triplicates of each volume were performed through SPE. These solutions yielded similar recoveries of ATCA and ATZA. Because 5% NH_4OH/MeOH was relative easy to air-dry, it was selected as the final elution solution for SPE.

Optimal SPE procedure for ATCA extraction

Various SPE procedures were tested and the best recovery was obtained using the procedure below. Mice plasma or homogenized mice organs (200 μL) mixed with 20 μL of internal standard (ATZA) was diluted with 800 μL of 10 mmol/L phosphate buffer (pH 7.4). ATCA and ATZA were then extracted with and eluted from the MCX cartridge. The samples eluted by the final elution solution were dried under gentle air streams. After air drying, the residues were reconstituted with 220 μL of mobile phase. Standard solutions and samples were then sonicated for 5 min prior to LC-MS/MS analysis. With a volatile organic additive, such as TFA, in the mobile phase, it is challenging to keep its concentration a constant from batch to batch. A precise control of TFA concentration, or elimination of matrix components could be investigated for method development, however, it is more applicable to just use an internal standard for calibration in our method.

Use of TFA as an additive in mobile phase

In our previous studies using ESI/MS/MS, a mobile phase of 0.5% acetic acid gave a good yield of the MRM transition ion of m/z 147 → 101 for the detection of ATCA. This mobile phase was found to be a poor eluent of ATZA. However, as shown in Figure 3, when TFA was added to the mobile phase a good sharp ATZA peak was detected. This result suggested that TFA was a more effective ion-paring reagent than acetic acid during the chromatography. Therefore, 0.5% TFA/MeOH was selected as the mobile phase, replacing the 0.5% acetic acid/MeOH mobile phase used in our prior work.

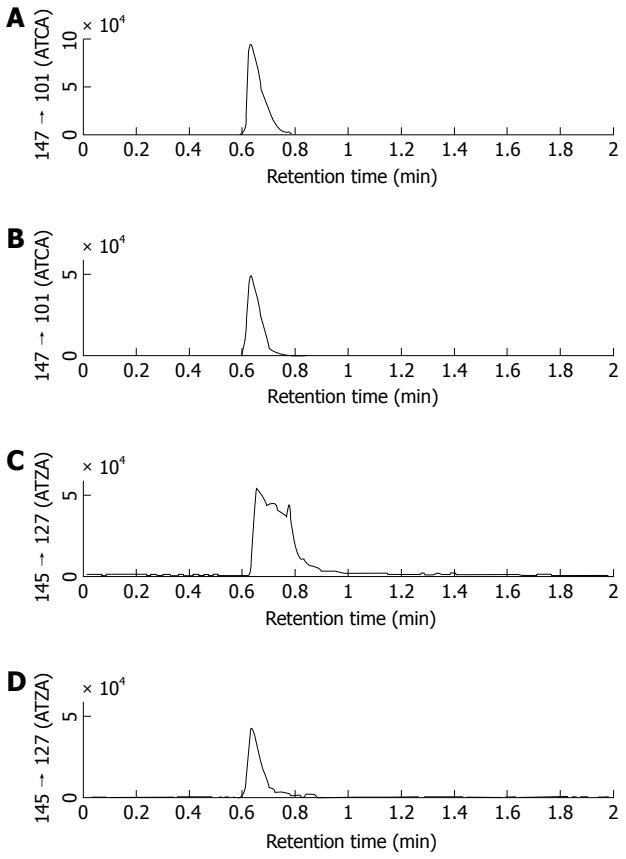


Figure 3 Comparison of chromatograms of 2-aminothiazoline-4-carboxylic acid and 2-aminothiazole-4-carboxylic acid obtained by using 0.5% acetic acid/MeOH as mobile phase (A and C) and 0.5% trifluoroacetic acid/MeOH as mobile phases (B and D). When trifluoroacetic acid (TFA) was added to the mobile phase a good sharp 2-aminothiazole-4-carboxylic acid (ATZA) peak was detected. This result suggested that TFA was a more effective ion-paring reagent than acetic acid during the chromatography. Therefore, 0.5% TFA/MeOH was selected as the mobile phase, replacing the 0.5% acetic acid/MeOH mobile phase used in our prior work. ATCA: 2-aminothiazoline-4-carboxylic acid.

Use of ATZA as the internal standard

ATCA standard solutions, ranging from 0-1000 ng/mL, were analyzed by LC-MS/MS with ATZA as the internal standard. External calibration curves were first constructed to show the relationship between ATCA concentrations and integrated ATCA LC-MS/MS peak areas. As shown in Figure 4A, the external standard calibration curves showed good linearity over the tested ATCA concentration range with average R^2 = 0.999 in a between-days experiment. The dashed lines show linear regression of calibration in each day. These linear regression lines yielded an average calibration equation y = (199 ± 60) × (n = 4), relative standard deviation (RSD) of calibration slopes = 30%. The high %RSD of the slopes indicated a typical ionization suppression effect of ESI. Internal calibration curves were next prepared by plotting the ratio

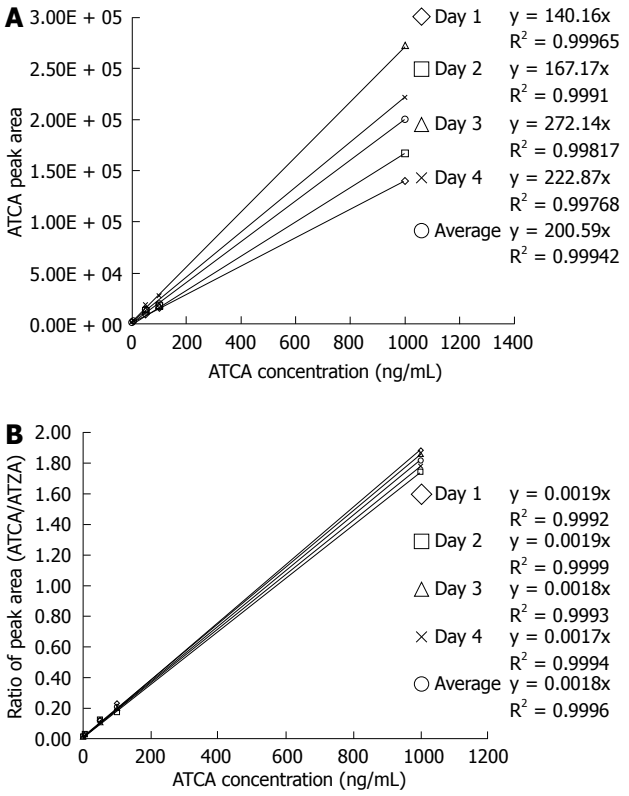


Figure 4 External calibration curves, without using 2-aminothiazole-4-carboxylic acid as the internal standard (A) and internal standard calibration curves constructed using 2-aminothiazole-4-carboxylic acid as the internal standard (B). A: The external standard calibration curves showed good linearity over the tested 2-aminothiazoline-4-carboxylic acid (ATCA) concentration range with average R^2 = 0.999 in a between-days experiment. The dashed lines show linear regression of calibration in each day. These linear regression lines yielded an average calibration equation y = (199 ± 60) × (*n* = 4), relative standard deviation (RSD) of calibration slopes = 30%. The high %RSD of the slopes indicated a typical ionization suppression effect of electrospray ionization. Internal calibration curves were next prepared by plotting the ratio of ATCA to 2-aminothiazole-4-carboxylic acid (ATZA) peak areas *vs* ATCA concentration; B: Ratioing to the internal standard peak area improved the reproducibility of the calibration curves. The dashed lines show calibration curves obtained on different days. These internal standard compensated calibration curves yielded an average calibration equation y = (0.018 ± 0.00007) × (*n* = 4), RSD = 4%. The decrease of the RSD from 30% (external calibration) to 4% (internal standard calibration) demonstrated that the internal standard, ATZA, enables effective compensation for ionization suppression and matrix effects, and substantially improves the precision with which ATCA can be quantified.

of ATCA to ATZA peak areas *vs* ATCA concentration. As shown in Figure 4B, ratioing to the internal standard peak area improved the reproducibility of the calibration curves. The dashed lines show calibration curves obtained on different days. These internal standard compensated calibration curves yielded an average calibration equation y = (0.018 ± 0.00007) × (*n* = 4), RSD = 4%. The decrease of the RSD from 30% (external calibration) to 4% (internal standard calibration) demonstrated that the internal standard, ATZA, enables effective compensation for ionization suppression and matrix effects, and substantially improves the precision with which ATCA can be quantified. The effect of matrix components on MS/MS signals could be determined by comparing the

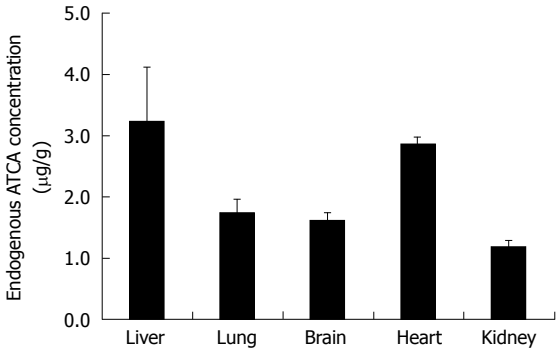


Figure 5 Endogenous level of 2-aminothiazoline-4-carboxylic acid in mice organs. The endogenous levels of 2-aminothiazoline-4-carboxylic acid (ATCA) in different organs of mice were measured using the solid phase extraction procedure and LC-MS/MS conditions outlined above. Triplicate samples from healthy mice showed endogenous ATCA concentrations as follows: 1.2 ± 0.1 μg/g for kidney samples, 1.6 ± 0.1 μg/g for brain samples, 1.8 ± 0.2 μg/g for lung samples, 2.9 ± 0.1 μg/g for heart samples, and 3.6 ± 0.9 μg/g for liver samples.

slope of internal standard calibration curves and matrix added calibration curves (e.g., standard addition). However, it could not eliminate matrix effect for the different biological samples. Note that the use of an internal standard does not mean that the method is interference-free.

Endogenous level of ATCA in mice organs

The endogenous levels of ATCA in different organs of mice were measured using the SPE procedure and LC-MS/MS conditions outlined above. As showed in Figure 5, triplicate samples from healthy mice showed endogenous ATCA concentrations as follows: 1.2 ± 0.1 μg/g for kidney samples, 1.6 ± 0.1 μg/g for brain samples, 1.8 ± 0.2 μg/g for lung samples, 2.9 ± 0.1 μg/g for heart samples, and 3.6 ± 0.9 μg/g for liver samples.

DISCUSSION

Mobile phase composition can impact the ESI ionization of analytes[27], The responses of positive ions may be varied by changes in the electrolyte concentration, pH, and percent methanol at the ESI ionization source[28]. TFA has been known to suppress ESI[29]. For quantitative analysis, it is important to air-dry the ATCA and ATZA standard solutions so that all solutions can be redissolved in the same batch of mobile phase (freshly prepare mobile phase is recommended). This ensures reproducible ionization suppression from sample to sample. We found that this solvent reconstitution step increased the precision of signal from replicate standard solutions (%RSD of ATCA < 5% and %RSD of ATZA < 8%). Note that the ring in ATCA may open under heat and basic conditions[24]. The evaporation of solvent should be performed under ambient temperature.

Matrix components in the sample could interfere with the detection of ATCA in LC-MS/MS. SPE was used to isolate the analyte from the complex sample matrices. However, while SPE generally reduces matrix effects, it can under certain circumstances also magnify matrix ef-

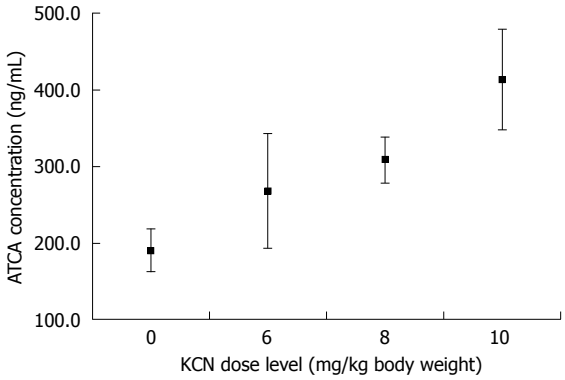


Figure 6 2-aminothiazoline-4-carboxylic acid concentration in mice plasma after different doses of potassium cyanide (endogenous level = 0 mg/kg body weight dose of potassium cyanide). Mice received three different sublethal doses (6, 8 and 10 mg/kg) of cyanide subcutaneously (3 mice/doses) and were terminated 15 min after cyanide exposure. A significant correlation of cyanide dose *vs* 2-aminothiazoline-4-carboxylic acid (ATCA) concentration in plasma samples was observed. ATCA concentration in mice plasma samples was increased from 189 ± 28 ng/mL (n = 3 mice) for endogenous level [0 mg/kg body weight dose of potassium cyanide (KCN)] to 413 ± 66 ng/mL (n = 3 mice) for 10 mg/kg body weight dose of KCN.

fects[30], an internal standard was needed to minimize this deviation of calibration. Ideally, the choice of deuterated ATCA as the internal standard has advantages chromatographically and can eliminate limitations of chemical properties in separation and detection method development. Unfortunately, deuterated ATCA was not commercially available. From this work, ATZA was selected and proved as to be a good alternative as an internal standard. The use of ATZA as an internal standard successfully mitigated ESI suppression and matrix effects. Note that the difference in the chemical properties of ATZA and ATCA has been shown by the difference in MS/MS fragmentation and the pKa of ATZA is different from ATCA which potentially can be a problem in separation. Fortunately, ATZA co-eluted with ATCA in our method. This is advantageous because ion suppression at the ESI source should then be more uniform for both ATCA and ATZA.

It has been suggested in an *in vivo* study that the reaction of an oxidized disulfide with a sulfur nucleophile from glutathione could be a plausible origin for ATCA[27]. It is likely that endogenous levels of ATCA in each organ reflect the availability of disulfide and the concentration of glutathione in those organs. Thus, endogenous ATCA levels may give an estimate of each organs capacity for cyanide detoxification. For example, the preliminary results showing lower endogenous ATCA levels in the kidneys and brain may be consistent with lower capacity for cyanide detoxification in those organs. This lower capacity might be partially due to the absence of rhodanese enzymes in the kidney and brain.

Mice received three different sublethal doses (6, 8 and 10 mg/kg) of cyanide subcutaneously (3 mice/doses) and were terminated 15 min after cyanide exposure. As shown in Figure 6, a significant correlation of cyanide dose *vs* ATCA concentration in plasma samples was observed. ATCA concentration in mice plasma samples was increased from 189 ± 28 ng/mL (n = 3 mice) for endogenous level (0 mg/kg body weight dose of KCN) to 413 ± 66 ng/mL (n = 3 mice) for 10 mg/kg body weight dose of KCN. This data represents the first *in vivo* study of ATCA concentration levels in plasma samples following administration of various controlled doses of cyanide.

Present *in vivo* study confirmed that ATCA concentration in plasma samples rose significantly with increasing cyanide dose levels in a mice model. This finding suggests that ATCA has the potential to serve as a plasma biomarker for cyanide poisoning. However, further studies for detecting ATCA in biological samples after exposure of various cyanide doses employing various animal models are necessary to reaffirm that ATCA can be established as a suitable cyanide biomarker/forensic biomarker. Since it is previously proven that ATCA is a persistent, chemically stable metabolite[26], more over the formed ATCA concentrations are significantly enhanced in certain organs even after a lower dose of cyanide exposure[25], This method can also be readily applied to actual autopsy materials. It is important to develop this method into a complementary method to extend the detection time window for cyanide poisoning cases, especially for those autopsy samples that have been stored for a long time where cyanide poisoning was suspected. These studies are superior to the previously reported studies with a different animal model (rat)[25]: While the previous experimental setup of applying one single KCN dose (4 mg/kg) did not prove the potential importance of ATCA as a plasma biomarker, present studies confirm that at higher doses of KCN administration the plasma ATCA level is proportionally and significantly increasing with increasing KCN doses. Earlier studies indicated enhanced ATCA levels in the urine and plasma[20] of smokers *vs* non smokers, suggesting that ATCA has potential as a cyanide biomarker in human. Different cyanide metabolite baseline levels in smokers *vs* nonsmokers is a factor that needs to be accounted for in all methods, including ATCA based methods, that seek to differentiate between chronic and acute cyanide exposure. Present findings provide additional evidence to the study by Logue *et al*[20], for the potential of ATCA to serve as a plasma biomarker in mice and human, and confirm its utility as a forensic biomarker what was in agreement with the earlier investigation using a single lower dose of KCN in a rat model[29].

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COMMENTS

Background

Cyanide (CN) is a potent poison, which people can be exposed to in a various ways. It has been widely recognized as a chemical warfare agent and is considered as a possible terrorist threat. It is important to determine cyanide itself, or its metabolites in biological matrices for forensic, clinical, military, research

and veterinary purposes. Common metabolites of cyanide include 2-aminothiazoline-4-carboxylic acid (ATCA) and thiocyanate. ATCA is formed when cyanide reacts with cysteine.

Research frontiers

One of the most important frontiers in cyanide research to develop effective methods for forensic analysis of cyanide exposure, based on detection of CN and its metabolites (thiocyanate and ATCA). Since cyanide is present in the body in the volatile hydrogen cyanide form, it is rapidly depleted from blood (generally within the first 20 min of exposure) following exposure, leaving only metabolites as biomarkers. Important criteria for a biomarker include chemical stability, and biomarker concentration levels in biological matrices that correlate with the doses of exposure. Earlier studies proved that ATCA is a chemically stable cyanide metabolite. The present study indicates the cyanide dose *vs* ATCA blood concentration relation, therefore it suggests that ATCA might be established as a cyanide biomarker.

Innovations and breakthroughs

Logue *et al* (2005 and 2010) reported an analytical method gas chromatography-mass spectrometry (GC-MS) to measure ATCA in biological matrices. Since ATCA is not volatile, it requires derivatization prior to measurement *via* GC-MS. The authors' HPLC method detects ATCA without derivatization. For sample preparation before injecting the samples to the chromatography column (LC-MS/MS method), Yu's group at SHSU (Jackson *et al*, 2010) developed and reported a molecularly imprinted polymer stir bar sorption extraction for determining ATCA. The present study employs the LC-MS/MS method, and it compared the two extraction methods (molecularly imprinted polymer stir bar sorption extraction and SPE), and for further analysis it recommends the SPE extraction when determining ATCA by LC/MS/MS method. Employing the HPLC/MS/MS method with SPE extraction, this study confirmed that ATCA can serve as a biomarker for cyanide exposure. In an earlier study (Petrikovics *et al*, 2011) reported the possible establishment of ATCA as a forensic biomarker, since the post exposure concentration of ATCA in organs was significantly elevated relative to the endogenous ATCA levels, especially in the liver in a rat model. Further investigations are being pursuedto determine endogenous cysteine/cystine levels in order to understand why certain organs contain more ATCA after a constant cyanide exposure. When a constant low dose of cyanide was administered, the plasma ATCA level was not elevated relative to the endogenous plasma ATCA. In the present study the authors report that when cyanide doses are higher, and more representative of acute exposure, the ATCA levels in the plasma are correlated with CN dose in a mice model.

Applications

This results of this study suggest that ATCA holds promise as a forensic biomarker for CN.

Peer review

The results of this study show that ATCA levels are strongly correlated with CN exposure levels in a mice model. These results are consistent with the hypothesis that ATCA might serve as a biomarker/ forensic biomarker for cyanide exposure.

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AGA Clinical Congress of Gastroenterology and Hepatology: Practice, Evidence and Quality in 2012
Miami, FL, United States

January 26, 2012
Symposium of the Swiss Society of Pharmacology and Toxicology, Advances in Pharmacology - Cardiovascular Pharmacology
Bern, Switzerland

January 28 – February 1, 2012
LabAutomation2012
Palm Springs Convention Center, Palm Springs, CA, United States

February 1-4, 2012
3rd International Workshop on Medical Image Analysis and Description for Diagnosis System
Hotel Tivoli Victoria, Algarve, Portugal

February 24, 2012
State Stem Cell Agency Governance Subcommittee
San Francisco, CA, United States

March 11-14, 2012
Thoracic Imaging 2012
Hyatt Regency, Huntington Beach Resort and Spa, Huntington Beach, CA, United States

March 25-30, 2012
44th International Diagnostic Course Davos (IDKD)
Davos, Switzerland

April 26-29, 2012
75th Anniversary of the Canadian Association of Radiologists Annual Scientific Meeting
Le Centre Sheraton, Montreal, Quebec, Canada

April 29 - May 4, 2012
EUCHEM Conference on Stereochemistry
Brunnen, Switzerland

May 4-6, 2012
World Congress on Biotechnology
Hyderabad, India

June 7-9, 2012
ASCI 2012 - 6th Congress of Asian Society of Cardiovascular Imaging
Bangkok, Thailand

June 9-13, 2012
2012 Annual Meeting of the Society of Nuclear Medicine
Miami Beach, FL, United States

August 15-19, 2012
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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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REVIEW

Protein dynamics *via* computational microscope

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Abstract

The purpose of this overview is to provide a concise introduction to the methodology and current advances in molecular dynamics (MD) simulations. MD simulations emerged as a powerful and popular tool to study dynamic behavior of proteins and macromolecule complexes at the atomic resolution. This approach can extend static structural data, such as X-ray crystallography, into dynamic domains with realistic timescales (up to millisecond) and high precision, therefore becoming a veritable computational microscope. This perspective covers current advances and methodology in the simulation of protein folding and drug design as illustrated by several important published examples. Overall, recent progress in the simulation field points to the direction that MD will have significant impact on molecular biology and pharmaceutical science.

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Key words: Molecular Dynamics; Computer simulations; Protein folding; Force field; X-ray crystallography

INTRODUCTION

The understanding of functions of biological macromolecules has relied not only on the structural data but also their dynamical behavior. The early view of the proteins as relatively rigid structures has been replaced by a dynamic model. In these models conformational changes and motions play an essential role in their function. In the last 25 years, biomolecular simulations has become a powerful tool to trace atomic motions of protein and DNA molecules and yielded important insights into molecular mechanisms[1-3]. The molecular dynamics (MD) simulation is considered a pivotal methodology to access dynamical behavior of macromolecules *in silico*. This technique provides ultimate atomic resolution details about the dynamic properties of the system as a function of time. It offers connection between the structure and function by enabling the exploration of the conformational space and energy landscape available to protein molecules. It is not surprising that the term "computational microscope" has been accepted by the scientific community[4].

One of the first MD simulations of proteins, bovine pancreatic trypsin inhibitor (BPTI), was reported in 1977. This work should be considered as the first attempt to utilize computer simulation to observe protein motions at 9.2 picosecond (ps) time scale[5]. In 1988, eleven years later, the same protein was simulated for 210 ps using explicit solvent[6]. The latter work showed good correlation between the average structure produced by simulation and the high-resolution X-ray structure, emphasizing the importance of longer simulation

time and use of explicit water molecules. Since then the dramatic increase in computational power and significant improvement in methodology made the simulation much more accurate and stable. It is now routine to run simulations from 100 ns (10^{-7} s) to several μs (10^{-6} s) where even shorter time scales (10-100 ns) can well describe local dynamics of the proteins structures. Experimental measurements show that rotation of protein side chains often occurs around 0.5 ns timescale ["Physical Biology of the Cell", Rob Phillips, Jane Kondev and Julie Theriot (2009) and references therein]. However, since many functionally important biological events occur on timescales of many microseconds or milliseconds, including protein folding, protein-protein or protein-drug interactions, much longer time scales are needed for conformational sampling. Recently, there were a large number of efforts to extend simulations to a longer timescales by designing specialized hardware to speed up MD simulations and/or by improving the code[7-9]. The longest MD simulation published to date is a millisecond (ms) [1000 microsecond (μs)] simulation of the BPTI protein on a special-purpose supercomputer (called Anton) designed for MD simulations[10-12]. This work showed that BPTI transitioned reversibly among a small number of structurally distinct states with two states in the simulation accounting for 82% of the trajectory which agreed well with experimental data. Such behavior could not be observed at shorter (μs) timescales and thus confirms the importance of adequate simulations times.

The MD relies on the solution of the equations that describes the motion of the molecular system. In explicit, all-atom simulations, thousands to millions of individual atoms, representing, for instance, all atoms of the protein and surrounding water molecules, move in a series of short [e.g., 2 femtoseconds (fs)], discrete time steps. The MD trajectory represents the sequential set of time-evolved snapshots of atomic coordinates and generally provides data only at the level of atomic positions, velocities and single-point energies. The application of statistical thermodynamics allows to obtain macroscopic properties such as pressure, heat capacity and free energies of the system. The product is a detailed "movie" of molecular behavior over time. As a result, MD has became a tool for researches to investigate structural aspects, kinetics and thermodynamics of various macromolecule systems, including the dynamics in enzyme activity[13-15], transport of ion and small molecules[16-18], protein-protein and protein-DNA interactions [19-21], protein folding[22,23] and ligand-target interactions[24-27], just to mention a few. In general, each step in MD simulations consists of computationally intensive force calculations, followed by a less expensive integration step that advances the positions of the atoms according to classical laws of motions. Forces for each atom of the system are calculated based on the molecular mechanics equations. The functional form of such equations is shown in Figure 1. The potential energy parameters (bond lengths, vibrational energies, force constants, atomic and partial atomic charges, proper van der Waals atomic radii, *etc.*) are derived empirically from experimental techniques such as spectroscopy and X-ray crystallography, and also from ab initio quantum mechanical calculations. Collectively, these parameters describe the contributions of various atomic forces that govern MD and are called a 'force field'. There are several well established force fields which are currently being used and continued to be developed. The Chemistry at HARvard Macromolecular Mechanics (CHARMM) biomolecular force field developed by Karplus *et al*[28,29] is widely used for the simulation of proteins and other many particle systems using CHARMM and NAMD molecular simulation programs[30]. The Assisted Model Building with Energy Refinement (AMBER), developed by the Kollman group[31], is a set of molecular mechanical force fields for the simulation of biomolecules, which was initially developed for the nucleic acids and now adopted for the simulation of a wide range of the biomolecules, including proteins. AMBER has a package of molecular simulation programs and can also be used by NAMD. There are several others that are available, including the Energy Calculation and Dynamics (ENCAD) developed by Levitt [32], the GROMOS and the hydrocarbon force fields (MM2-4)[33]. ENCAD and CROMOS force fields are available through the Groningen Machine for Chemical Simulations computational package[7]. In general, the force fields express the total force on an atom as a sum of 3 major components: bonded forces which involve interactions between small groups of atoms connected by one or two covalent bonds; van der Waals forces which include interactions between small groups of atoms in the system; and electrostatic forces which include interactions between all pairs of atoms (non-bonded pair-wise interactions) (see the functional form of AMBER equation, Figure 1). Chemical bonds and atomic charges are modeled using simple harmonic motions, and dihedral angles are modeled using a sinusoidal function that approximates the energy differences between eclipsed and staggered conformations. The non-bonded forces arise from van der Waals forces and electrostatic interactions. The non-bonded energy terms between every pair of atoms increase as the square of the number of atoms for a pairwise model (N^2) and represent largest summation term in the potential energy equation. This part of the simulations is the most computationally expensive. The van der Waals forces fall quickly with the distance and in computer simulations are treated with 12/6 Lennard-Jones potentials. To reduce the cost of calculations the contributions from these forces can be controlled by the user defined cutoff distance. The very short cutoff (~4 Å) does not adequately model the properties of the system when a very long cutoff (over 20 Å) significantly increases simulation time and has been shown not to improve fidelity of the simulation over the intermediate values around 9-12 Å which are commonly used in the modern simulation[34]. The electrostatic forces fall off slowly with distance and truncation at cutoff distance introduces significant errors in the simulations. Electrostatic forces, modeled using Coulomb's

law, are typically computed using approximate methods (such as Ewald summations) that account for long-range effects with the explicit interaction of all pairs of atoms[35,36]. However, recent studies showed that use of approximation methods could affect the results of the simulations. For example, in case of the protein folding using short (9 Å) cutoff distances could shift the balance between hydrophobic and hydrophilic interactions leading to stabilization of the more compact structures[37]. Moreover, the neglect to include long-range component of the Lennard-Jones interactions and the lack of highly accurate treatment of the long-range electrostatics could result in artifacts during the folding pathways. In contrary, the free energy of the protein folding and structural properties of the folded protein are relatively unaffected by these approximations[37]. The level of the approximations used in MD simulations should depend in part on the goal and questions that these calculations are planned to address.

The common protocol for performing MD simulations consists of a number of steps and is shown in Figure 2. In simulations of biomolecules, an X-ray crystal structure or an nuclear magnetic resonance (NMR) structure is first obtained from the Brookhaven Protein Databank to be commonly used as the initial structure. It is also possible to use a theoretical structure developed by homology modeling (also known as comparative modeling) or extended protein sequence if the researcher desires to investigate protein folding. Prior to starting MD simulation, it is recommended to perform energy minimization of the structure to remove any strong van der Waals interactions which might exist in the initial structure. These unwanted interactions can lead to local structural distortion resulting in an unstable simulation. At this point, explicit water molecules are added to solvate the system. Another energy minimization with the macromolecule fixed should follow the solvation step to allow the added water molecules to readjust around the protein molecule. At this point, the initial velocities at a low temperature are assigned to each atom of the system and Newton's equations of motion are integrated to propagate the system in time. In explicit solvent simulation, the protein position is fixed initially to allow equilibration of water molecules. Once that is done, the constraints on the protein can be removed and the whole system (macromolecule system and waters) can evolve in time. At the beginning of simulations velocities are assigned at low temperature and simulation proceeds *via* heating phase. Periodically, if needed, new velocities are assigned at a slightly higher temperature and the simulation is allowed to continue. This is repeated until the desired temperature is reached (commonly around 300-310 K). Once the desired temperature is reached, the equilibration simulation of the system continues and properties such as structure, pressure, temperature and energy are monitored. The purpose of equilibration dynamics is to run the simulation until these properties become stable with respect to time. If the temperature increases or decreases significantly, the velocities can be scaled such that the temperature returns to near its desired value. The final step of the simulation is to run the simulation in "production" phase for the desired time length. This can be from several to 10^6 ns. The MD trajectories from the production dynamics can be analyzed and post-processed to obtain conformational dynamics, thermodynamic parameters and free energy values for the system of interest. There are many modifications of the procedure described above using different protocols to control the temperature and generate MD trajectories. The additional details on MD procedures and theory can be found elsewhere[38-40]. The new methods such as replica-exchange MD (REMD) have been developed and employed for the simulation of macromolecules[41]. A series of replicas are run in parallel at temperatures ranging from a desired temperature to a high temperature at which the replica can easily overcome small energy barriers[42]. The REMD approach can overcome the multiple-minima problem known to trap structures in the local conformational minimum by exchanging non-interacting replicas of the system at several temperatures.

The vast increase in the number of MD papers published in the last 10 years, including publications in those highly respected journals such as Nature and Science, is a clear evidence that MD simulations become a widely accepted tool for investigation of conformational features for biological macromolecules. The number of publications using MD is now in tens of thousands. For example, using "molecular dynamics" and "proteins" as topic words to search ISI "web of science" (http://apps.webofknowledge.com/) yielded almost 4000 papers in 2011 *vs* about 1200 articles in 2001. Therefore, it is impossible for such a short review to adequately describe all major work done using MD simulations. Here we chose to describe a small number of specific examples to illustrate the use of the MD simulations to obtain functionally relevant information.

MD AND PROTEIN FOLDING

Understanding the protein folding or how the polypeptide chain is able to fold to its native conformation is essential to the description of the function of the protein. It is well established that misfolding is present in a variety of diseases[43]. One of the key aspects of the protein folding is the mechanisms by which the protein finds the native conformation despite enormous number of statistically possible conformations. In addition, the folding is slow on the simulation time scale with many proteins taking microseconds to fold. So far only small sized proteins (10 to 80 amino acid residues), with no disulfide bonds or prostatic groups, have been successfully folded to its native conformation. The small sizes and rather short folding times of such proteins make them good candidates for MD simulation using all-atom models in explicit solvent since the native conformation of these proteins is determined solely by the protein amino acid sequence[44]. The recent work from the DE Shaw group[45] summarized the simulations of 12 proteins

$$V = \sum_{bonds} k_b(l-l_o)^2 + \sum_{angles} k_a(\theta-\theta_o)^2 + \sum_{torsions} \frac{1}{2}V_n[1+\cos(n\omega-\gamma)] + \sum_{j=1}^{N-1}\sum_{i=j+1}^{N}\left\{\varepsilon_{i,j}\left[\left(\frac{r_{o,ij}}{r_{ij}}\right)^{12} - 2\left(\frac{r_{o,ij}}{r_{ij}}\right)^{6}\right] + \frac{q_i q_j}{4\pi\varepsilon_o r_{i,j}}\right\}$$

Figure 1 An example of the equation used to calculate atomic forces. The equation describes potential energy in the Assisted Model Building with Energy Refinement force field. The first summation term represents the energy between the covalently bonded atoms. Summing of the angles, second term, represents the energy due to the angle geometry. Third term represents the energy of the torsion angles. Forth term accounts for the energy of the non-bonded interactions between all pairs of atom. This term can be decomposed into van der Waals and electrostatic energies. The subscript zero represents equilibrium values. The energy terms are parameterized to fit experimental (for example, spectroscopic) data and/or quantum-mechanical calculations.

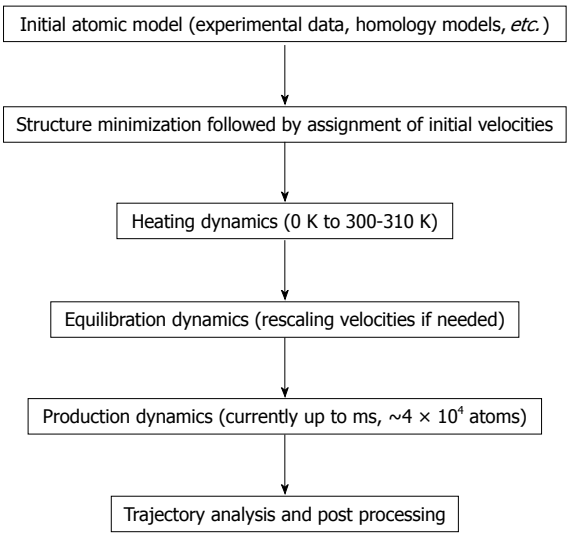


Figure 2 General steps used in molecular dynamics simulations. During the simulations molecular focus on each atom are calculated based on the equation shown in Figure 1. During dynamics calculations (heating, equilibration and production) the positions of atoms are moved according to Newton' s law of motion. The simulation time is advanced, and the process is repeated numerous times to generate molecular dynamics rajectory. The longest trajectory is generated during the production run.

which represent three major structural classes (α-helical, β-sheet and mixed α/β). All simulations started from extended conformations to avoid bias toward the native state. In that work total of approximately 8 ms of MD simulations were collected. Figure 3 shows the representative structures of those 12 proteins. For each protein MD folded structure is shown in blue and superimposed on the experimental determined structure. For most of the structures (8 out of 12) the root mean square deviations of Cα atoms (Cα-RMSDs) between the two structures, which includes flexible tails residues, were below 2 Å, indicating an excellent agreement between experiment and simulation. To confirm the finding of this work, simulations were performed near the melting temperature, at which both unfolding and folding could be observed repeatedly bringing total to 10 unfolding and 10 folding events for each protein[45]. The authors collected about 400 folding and unfolding events for a total of 8 ms of simulation. The proteins exhibiting larger RMSD values (BBL, protein B, homeodemain and α3D) all contain 3 α-helices. It is possible to suggest that this could indicate minor imperfections of the force-field, however, it is also possible to assume that the experimentally determined conformations for these proteins depend on experimental conditions[46,47]. Deviations between the MD and experimental data might represent differences between the protein's structure at the simulated temperature and the lower temperatures used for experimental structure determination. Based on the MD simulations reported by Lindorff-Larsen *et al*[45], the authors were able to propose general principles that underline protein folding. They concluded that the pathway toward the native conformation occurs *via* formation of the key long-range contacts at the early stages of the folding. These contacts support secondary structure elements which are only formed in the unfolded state. Nine out of 11 proteins simulated in that work share more than 60% of the native contacts formed at any given time during the folding process. The formation of number of structural elements was observed in the similar order, suggesting a common folding pathway for the proteins studied. It is reasonable to propose that heterogeneous folding process for various proteins share a large fraction of structural features and could belong to the same folding "route". The examination of the thermodynamics and kinetics of the folding process showed the absence of a distinct free-energy barrier for folding and the analysis yielded multiple barriers along the folding path which were less than 4.5 k_BT. Under experimental conditions corresponding to those used in above simulations folding of the protein was also not determined by single, well-defined free-energy barrier.

Recently, an all-atom MD simulations in explicit solvent, were used to describe the folding path of the 80 amino acid λ-HG mutant of λ-repressor fragment[48]. Using the temperature-dependent MD runs the authors showed that the folding of the λ-repressor is not a two-state process as suggested before. In addition, the authors proposed possible mutation sites which could lead to a fast -folding mutant.

The results described above demonstrated that the current molecule mechanics force fields and simulations protocols are accurate and reliable to make long-time scale MD simulations as a powerful tool for characterizing large conformational changes in proteins.

MD AND DRUG DISCOVERY

For the past 20 years drug discovery has already heavily relying on the computational methods. It is reasonable to predict that computational methods, such as MD simulation, will further advance drug-optimization and enhance our ability to select and design better molecules for the interaction with specific protein targets. It is well established that molecular recognition and drug binding are a very dynamic process. In solution, when a small molecule approaches a target, it deals with the macromol-

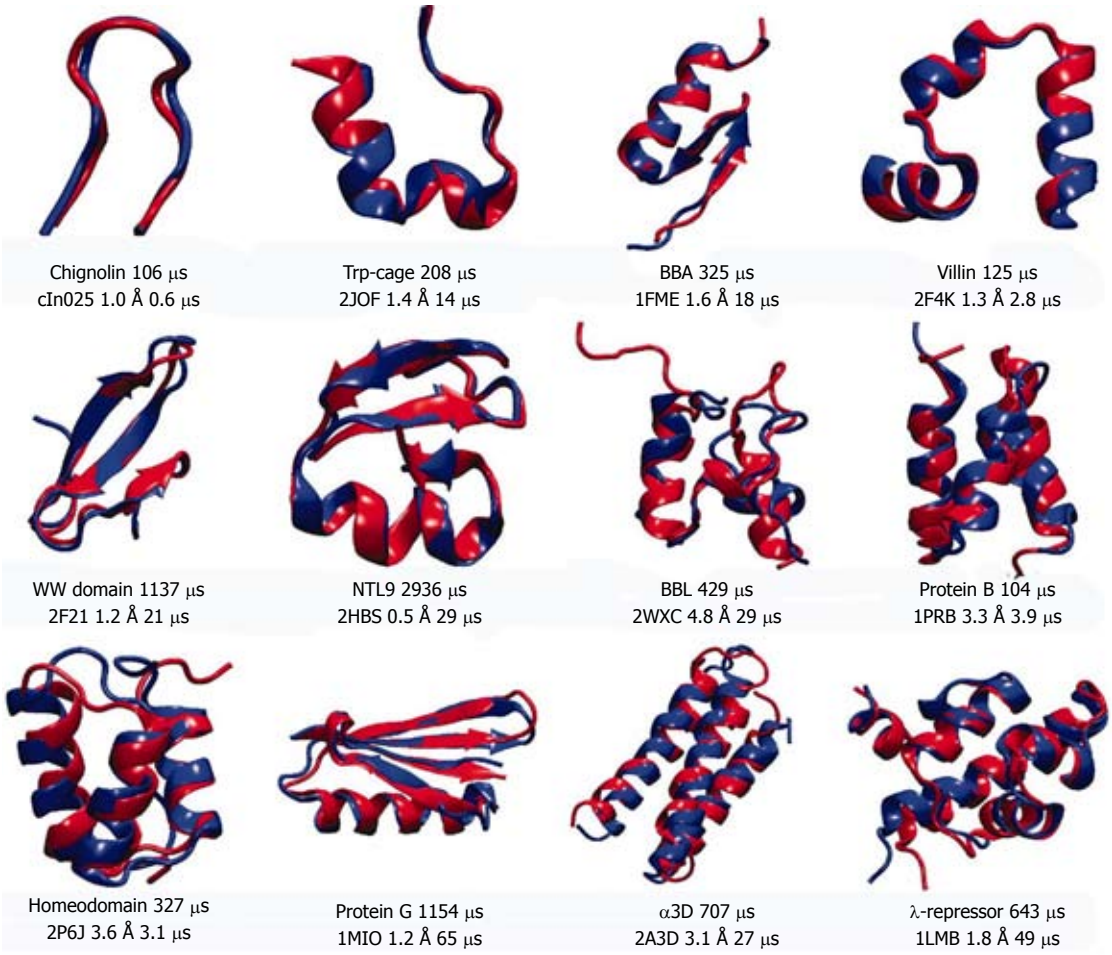


Figure 3 Representative structures of 12 proteins used in molecular dynamics simulation studies[42]. Experimentally determined structures are shown in red and superimposed onto the structures obtained from molecular dynamics simulations (shown in blue). Protein Databank (PDB) entry, root mean square deviations of Cα atoms between two structures and simulation times (total and needed for folding) are displayed for each protein under the superimposed structures. For Protein G the PDB entry was used for the closest homolog, since the structure for the simulated sequence has not been solved experimentally. Reproduced with permission (Copyright 2011, Science publishing group).

ecule in constant motions. Given that the static models produced by X-Ray crystallography and time-averaged structures by NMR tell little about protein dynamics, MD simulation can provide the dynamic picture of the interaction between the small molecule (such as a drug) and the target molecule. Upon binding, the ligand molecule may further induce conformational changes that are not typically sampled when the ligand is absent[49]. There are a number of examples in which binding pathways were successfully reproduced using MD simulations. The complete reconstruction of the binding process of the benzamidine molecule (a known inhibitor of serine proteases) to trypsin was achieved using 495 MD simulations of 100 ns each[50]. Out of 495 trajectories, 187 (37% of total) produced binding events with RMSD less than 2 Å from the crystallographic pose. The obtained binding paths revealed two metastable intermediate states (S2 and S3, Figure 4). The simulation showed that the inhibitor rolls on the surface of the protein prior to entry into the binding pocket (S3 to S4 transition, Figure 4). Using MD simulations the authors estimated the standard free energy of binding which was within 1 kcal/mol from the experimental value. Reconstruction of the protein-ligand binding process and identification of the transition states suggest that mutations to the transition-state residues may alter the binding kinetics of the inhibitor. Simulations of the binding of several β-blockers to two β-adrenergic receptors (G-protein-coupled receptor modulators, which constitute one-third of all marketed drugs) showed the atomic details of this pharmaceutically critical process in which drug molecules spontaneously bind to the G-protein-coupled receptors to achieve final poses matching those determined crystallographically[51]. The MD revealed dehydration of the ligand and receptor along the binding pathway that represents unexpected kinetic barrier to binding. Such work suggested how receptor/ligand dehydration, known to be a major factor for ligand affinity, might be modulated to affect drug binding kinetics. MD simulation can also be used to determine relative binding free energies between the drug candidate and target protein using Poisson-Boltzmann surface area methods[52,53].

Besides identification of pathways and kinetics of binding, MD simulation can be used to obtain the struc-

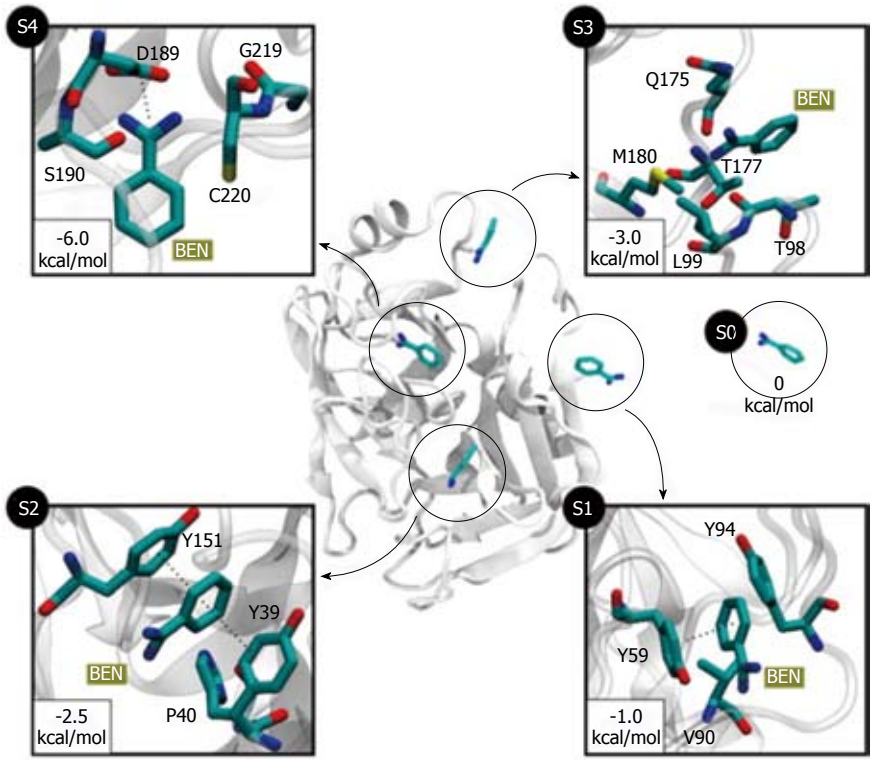


Figure 4 Five different metastable states (S0 to S4) identified for the benzamidine-trypsin complex[47]. The relative free energy between the unbound S0 and the bound S4 states is -6 kcal/mol. The most probable transition to the bound state S4 is from S3, since the barrier between two states is just 1.5 kcal/mol. In states S1 and S2, benzamidine is stabilized by π-π stacking interactions with Y151 and Y39 side chains. In S3, a hydrogen bond may be formed between the NH2 groups of benzamidine (only heavy atoms shown for clarity) and Q175 side chain, or by a cation-π interaction between the Q175 side chain and the benzamidine's benzene ring. Reproduced with permission (Copyright 2011, PNAS).

ture of the target using folding simulations, especially in cases where the structure of the target can not be obtained experimentally. Alternatively, simulation may be used to prepare homology models.

FUTURE DIRECTIONS

Since the millisecond barrier has been broken in MD, it is more than likely that we will be able to make testable predications about the key molecular processes at the atomic levels. Based on the current progress of all-atom MD simulations, a dramatic increase in the length of the generated trajectories should be expected in the nearest future. Parallel to the increase in the timescales accessible to the simulations, there has also been a growth in the size of the systems that can be studied. Much larger systems than those mentioned above have been already tested using MD simulations. These systems are comprised of several million atoms, such as bacterial ribosomes and viruses. In recent studies explicit solvent MD simulations showed essential conformational motions in the ribosome needed for the binding of aminoacyl-tRNA[54]. Such a system consists of 3.2 million atoms. This work showed that conformational motions of the 3'-CCA end of aminoacyl-tRNA resists simple accommodation (single lock-step mechanism), leading to a multistep accommodation process. The proposed mechanism and observed interaction pathways help to interpret large number of biochemical data and demonstrate that conformational changes during translation occur through a trial-and-error process, rather than in concerted lock-step motions. The 1 million atoms simulation of satellite tobacco mosaic virus (STMV) showed that the empty STMV capsid is not stable, thus explaining the failure of experimental efforts to prepare such empty capsids[55].

Although the conformational changes in the smaller system can be well described using MD simulations, the larger systems (5 millions of atoms or more) still pose many challenges. First, the biologically relevant timescales tend to increase as the system size increases. Second, the high-resolution structures are only available for relatively few very large macromolecule complexes[56]. The computational power to carry out simulation increases can be related to the Moore's law. This law describes how the performance of processors has been increasing exponentially over the last 50 years by doubling approximately every 2 years. Based on the application of the Moore's law to biological systems and without taking into account the design of special hardware architecture for MD, it has been proposed that for every 10-15 years in the past there was an increase of about three orders of magnitude in the timescale and about one and half orders of magnitude in the system size used by MD simulations[57] . Continuation of Moor's law suggests that processor computational power may increase by 1000 fold in the next 10-15 years. In addition

to enhanced processor integration, software and hardware advances will yield further increases. For example, recent application of the Graphic Processing Units (GPUs), together with the development of the general purpose GPU programming model called NVIDIA' s Compute Device Architecture, can significantly increase simulation times at fraction of CPU's cost and energy consumption. GPUs have been an integral part of personal computers for decades and their development and low cost has been strongly influenced by the entertainment industry. It has recently been shown that GPUs, due to their unique multiprocessor architecture, can greatly outperform their CPU equivalents. MD simulations can take advantage of GPU acceleration and achieve performance levels up to hundred times better than a single CPU core[58,59]. Based on the time frames obtained in the benzamidine binding studies, nowadays it is possible to reconstruct those binding pathways of 5 to 10 ligands per week on a moderately sized cluster of 32-64 GPUs[50].

It can be expected that within next 20-25 years it will be possible to simulate all-atom dynamics of a small bacterium and describe the complete set of processes within[25]. Such simulations can be probably performed for only few milliseconds or even less and would not provide much information due to large timescales needed for diffusions of macromolecules in bacterial processes. However, simulation of the part of a cell or fundamental pathways in molecular biology, such as protein synthesis, would be possible on the several seconds time-scales in the nearest future. It is obvious that macromolecule-macromolecule interactions are essential for biological processes. One major task in MD simulations is to carry out large-scale simulations of protein-protein and protein-DNA interactions. MD simulations will address the binding pathways between the macromolecules and how the ligand binding sites created, at the interface or at allosteric sites? Simulations can be expected for very large complexes such as the nuclear pore. Based on generated trajectories from such simulations it will be possible to observe passage of the delivery protein as it transits through a nuclear pore. In addition, MD will impose significant impact on the proteomics since the protein folding will be possible for larger proteins. Based on the current state of the MD simulations extrapolation suggests that folding of the 300 residues protein (over 10 ms simulation of approximately 100 000 atoms) will be possible within 10 years. Folding of the larger proteins, consisting of multiple subunits and over 1000 residues, will be still challenging and likely be achievable within 25 years[25]. Significant improvement of the timescales might come from omitting some motions in MD simulations. It might be possible to adequately sample conformational space without resolving all fast motions, thus reducing the computational power needed for the simulation of the particular system.

With constant gains in both computer power and algorithm design, MD simulation is expected to play an increasingly important role in the modern science from investigating the local motions in the biological macromolecules to the development of novel pharmacological therapeutics. This methodology has emerged as an integral part of molecular biology studies, providing a fundamental and reliable tool for experimentalists.

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January 20-21, 2012
AGA Clinical Congress of Gastroenterology and Hepatology: Practice, Evidence and Quality in 2012
Miami, FL, United States

January 26, 2012
Symposium of the Swiss Society of Pharmacology and Toxicology, Advances in Pharmacology - Cardiovascular Pharmacology
Bern, Switzerland

January 28 – February 1, 2012
LabAutomation2012
Palm Springs Convention Center, Palm Springs, CA, United States

February 1-4, 2012
3rd International Workshop on Medical Image Analysis and Description for Diagnosis System
Hotel Tivoli Victoria, Algarve, Portugal

February 24, 2012
State Stem Cell Agency Governance Subcommittee
San Francisco, CA, United States

March 11-14, 2012
Thoracic Imaging 2012
Hyatt Regency, Huntington Beach Resort and Spa, Huntington Beach, CA, United States

March 25-30, 2012
44th International Diagnostic Course Davos (IDKD)
Davos, Switzerland

April 26-29, 2012
75th Anniversary of the Canadian Association of Radiologists Annual Scientific Meeting
Le Centre Sheraton, Montreal, Quebec, Canada

April 29 - May 4, 2012
EUCHEM Conference on Stereochemistry
Brunnen, Switzerland

May 4-6, 2012
World Congress on Biotechnology
Hyderabad, India

June 7-9, 2012
ASCI 2012 - 6th Congress of Asian Society of Cardiovascular Imaging
Bangkok, Thailand

June 9-13, 2012
2012 Annual Meeting of the Society of Nuclear Medicine
Miami Beach, FL, United States

August 15-19, 2012
ICE 2012 - International Congress of Endoscopy
Daegu, South Korea

October 28-30, 2012
EANM 2012 - Annual Congress of the European Association of Nuclear Medicine
Milan, Italy

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The columns in the issues of *WJM* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide Guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in basic and clinical medical research methodology; (9) Brief Articles: To briefly report the novel and innovative findings in basic and clinical medical research methodology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJM*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of basic and clinical medical research methodology; (13) Guidelines: To introduce Consensuses and Guidelines reached by international and national academic authorities worldwide on the research basic and clinical medical research methodology; and (14) Voices: to publicize methodology-related communications that have been rejected or impossible for publication elsewhere due to evident prejudice and/or unreasonable reasons. Similarly, your experiences of the proven mistreatment during the past grant applications can be narrated or documented in this corner. The corresponding responses and echoes from readers are also welcome here.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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