Nano-scale drug processing simulation based on non-linear threshold model

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The use of micro-scale drugs in combating various diseases has been in clinical practice for centuries around the world. Today the use of diluted drugs, in wide ranges, is prevalent both in conventional and complementary therapies. Minute drug doses derived from viruses, bacteria, hormones, and other modified substances are extensively used in immunization and vaccination therapies. Anti-venom drugs are another example of diluted drugs in clinical use to counter fatal effects of venomous bites. Frequent, regular and continuous administration of small drug doses for a long time, such as used in metronomic therapies, is highly desirable in treating chronic diseases. A whole discipline of complementary medicine, known as homeopathy, is based on diluted drugs. Some toxicological scientists have been examining the beneficial effects of diluted substances, including attenuated radiation, in living organism for decades. Scientific studies have revealed that different physical and chemical properties of materials become more pronounced at nano-scale. This change of material properties at nano-scale makes dilution process a potential candidate for effective drug research discipline. All the existing methods to dilute drugs are based on Linear No-Threshold (LNT) model. The LNT model does not utilize any scientific metric such as Avogadro's constant or any other threshold point to terminate the dilution process. Such a drug dilution practice leads to a bottomless pharmacy, waste of resources and ambiguity in clinical practice. A new Non-Linear Threshold (NLT) model has been developed to quantize drugs at nano-scales. The NLT model accounts for the number of atoms or molecules presented in the starting seed of a drug based on Avogadro's constant. Initial simulation results showed that any drug could be quantized to a desired scale based on this model. Further simulation results show that all drugs can be quantized to a uniform standardized nano-level using NLT model. The NLT model is very useful to produce drugs for metronomic dosimetry to

treat cancer and other chronic diseases. This model will also help standardize homeopathic drugs to a certain uniform scale. Other immediate benefits would be preservation of resources, production of inexpensive drugs and fewer or no side effects to patients.

Introduction

There is an increased interest and demand in smaller drug doses for different clinical purposes ranging from immunization to metronomic therapy in cancer treatment [1-2]. However, these diluted bacterial and viral products used in vaccination and immunization procedures in conventional medicine are the mere percentage reduction of the original concentrations to their lower units. It has also been found that a regular, frequent and continuous administration of smaller drug doses for a long time in cancer patients has dramatic effects on their cure and survival rate [3-5]. This is known as metronomic therapy and a great deal of hope to cure chronic diseases, including resistant cancers, rests with this method [6]. This form of therapy could not be fully utilized because of the lack of dose standardization [5]. There has also been a consistent advocacy of the beneficial effects of the toxic chemicals and ionizing radiation at low doses known as hormesis [7-9]. Some advocates of hormesis have even suggested to regularly expose general population to smaller doses of ionizing radiation to boost their immune reaction [10]. Scientists and toxicologists have been questioning the LNT models in radiation protection and other environmental safety standards for decades. However, there is a wide range of chemical concentrations that can produce hormetic effects in different species. Again we do not have any analytical model to predict and formulate hormetic ranges for different toxic dilutions [11].

There is another therapeutic discipline, known as homeopathy, involved in diluted drugs worth mentioning at this point. The entire homeopathic pharmacy rests its foundation on drug dilutions [12]. These dilutions are not consistent with any scientific metric and lack general standardization [13]. The extensive applications of dilution processes in various therapeutic modalities require a critical analysis of the exiting drug quantization methods. Such a critical analysis will eventually help development methods for drug quantization for routine clinical practice in addition to preserve medicinal resources and maintain quality of nano-drugs. There are other compulsions to explore drugs at micro and nano scales. These include economic benefits, environmental preservations, and general safety of the patients associated with nano medicine utilizing diluted doses of the prescribed drugs. [14-16]

The emerging nano-technology has added a new dimension to this quest for new drugs at micro and nano scales for clinical applications [17-19]. The case to design and develop drugs at atomic or molecular levels has attained more prominence due to demonstrated claims that materials have elevated electrical, mechanical, chemical, magnetic, vibrational and other properties at nano-scale compared to their bulk-scale counterparts. The nano-scale processing technology needs to be precise and accurate to deliver optimal results. Drug quantization at nano-scale requires producing a drug with fewer atoms or molecules uniformly spread over a vehicle as a standard unit dose for therapy compared to our conventional bulk scale drug doses based on Maximum Tolerable Dose (MTD) model.

There is a growing need to explore and analyze dilution methods to quantize drugs at nano-scale that would be scientifically accurate, statistically reproducible, ecologically sustainable, environmentally friendly, economically affordable, clinically effective, therapeutically safe, technically feasible and globally available. I have described some drawbacks of the existing Linear No-Threshold (LNT) model in the next section. A Non-Linear Threshold (NLT) model has been suggested as a solution for nano-scale drug quantization to address some of the unresolved issues faced in LNT model.

Linear No-Threshold Model

All the existing dilution methods reduce the concentration of an original drug to a smaller percentage at some coarser levels. The only model that systematically dilutes drugs is practiced in homeopathic pharmacy. I would like to discuss the dilution methods based on this model. An LNT model was widely used by Samuel Hahnemann to dilute his homeopathic drugs. He maintained his 1:99 drug dilution ratio in a linear fashion known as centesimal scale. The method is crude in the sense that it has no threshold point to terminate the dilution process. Hahnemann was well aware of the shortcomings of his LNT model as he was getting inconsistent results with his diluted drugs. He finally tried another semi non-linear model, known as LM method, which was published in his post-mortem publication in 1921 [13]. Later, Hahnemann's disciple and the founder of the American Homeopathy, Hering, used the same LNT model except that the drug dilution ratio was modified to 1:9 scale known as decimal method. We observe a breakdown of these models for drugs diluted beyond Avogadro's limit. Similarly, if we try to incorporate three different drugs, such as Lithium, Arsenic trioxide (As_2O_3), and a larger molecule say with a

molecular weight of 1000 (i.e., Aco1000), starting with one gram of each drug, then we achieve a non-uniform drug dilution level throughout the process. All dilution processes run in parallel and do not converge at any point. This model provides non-uniform dilutions that can virtually run to infinity.

The most commonly used ratios in the homeopathic pharmacy are 1:9 and 1:99. A decimal method starting with an initial concentration of D1 diluted to a lower concentration of D2 is:

$$D_2=D_1/9 \text{ or } D_x= D_{x-1}/9 \qquad \text{where } x=2, 3, 4, 5,\ldots\infty. \qquad (1)$$

or for centesimal scale

$$D_2=D_1/99 \text{ or } D_c=D_{c-1}/99 \qquad \text{where } c=2, 3, 4, 5,\ldots\infty. \qquad (2)$$

In general this formula can be written for an LNT model as:

$$D_n=D_{n-1}/s \qquad (3)$$

where s is the dilution amount (i.e., s=9 for decimal scale and s=99 for centesimal scale) and n is the desired level of dilution. This is also known as serial dilution as the next level dilution is derived by mixing one part of the existing dilution with either 9 or 99 parts of alcohol, water or glucose.

For instance the 12^{th} decimal dilution will be derived by mixing one part of the 11^{th} level dilution with 9 parts of alcohol, water or glucose. Avogadro's constant is ignored in this model and there is no correction applied for density, temperature or other factors affecting the concentration of the final product. This model has no threshold point and the dilution process can continue infinitum. Furthermore, one can dilute drugs with a 100% probability of at least one atom or molecule of drug as an active ingredient in the final product to the 12^{th} level or the 24^{th} level dilution in decimal or centesimal scales respectively. This probability falls below unity in level 11 and level 22 for drugs with relatively larger molecules such as As_2O_3 as shown in Figure 1. However, the homeopathic pharmacy continues its dilution process much beyond these levels. This is the main reason that there is a great deal of skepticism about homeopathic pharmacy in the scientific community.

Another problem arises when we want to standardize two different drugs to a unique scale i.e., 30^{th} level of dilution. Since different substances have different atomic or molecular weights to start with, a single LNT model cannot uniformly standardize different drugs to a unique scale. Three different drugs, such as Lithium, Arsenic trioxide and a hypothetical drug, Aco1000, have

been simulated using LNT model. The simulation results are shown in Figure 2. These drugs cannot be standardized to a uniform scale with the existing LNT model.

Starting with one gram of each drug, adjusted for their atomic/molecular weights and diluted in decimal scales lead to different end levels. The probability of Lithium is higher at 22^{nd} dilution level whereas As_2O_3, and Aco1000 approach zero. Hence we cannot standardize drugs to a unique scale using LNT model.

b. Non-Linear Threshold Model

The proposed model starts by considering the number of atoms or molecules present in a mole of a drug also known as Avogadro's constant. The model is based on the concept that the fundamental entity responsible for any significant therapeutic effect starts with an atom or a molecule. All therapeutic effects created by any entity smaller than an atom or molecule (i.e., x-ray, heat, magnet, etc.) is beyond the scope of the present NLT model and is not the subject of this article. The presence of at least one atom or molecule of a substance is the limiting factor or threshold point for quantizing a drug. The inclusion of density accounts for the accuracy of the drug quantization process to a precise scientific level. This density is mainly of the attenuating substance such as water, alcohol or lactose since they are different in their atomic or molecular compositions from each other. The same volume of different solvents will dilute a drug to different levels. Furthermore, the effects of pressure, temperature, humidity, etc. have also been incorporated as correction factors for scientific accuracy. This method completely rejects any drug that is devoid of any chemical base or is purely imponderable such as x-ray, light, heat, magnet, dream, vacuum, etc.

Let us assume that a drug with a physical weight of w_m, and an atomic or molecular weight A_m, is required to be quantized to a nano-scale, S_n, where n is the quantization level. Given w_m gram of the particular drug in a solution an equation for first level drug quantization can be written as:

$$S_1 = (N_A.w_m)/(T.A_m)* C_f \qquad (4)$$

where N_A is the Avogadro constant, T is the starting seed for simulation, and C_f is the correction factor for temperature, pressure and density of the compound as $C_f=C_{t,p}.C_\rho$. $C_{t,p}$ is the correction factor for temperature and pressure. C_ρ is the correction factor for density of the compound.

Now any subsequent quantization level can be derived from the previous level as:

$$S_n=\lambda_n(S_{n-1}) \qquad (5)$$

where λ_n is known as Satti's Quantization Factor (SQF) based on n=2,3,4,5,….p-1. The factor n in equation 5 is the desired dilution level and p is the upper limit or threshold point for standardization. S_n is the new drug quantization level derived from the previous S_{n-1} level. SQF is computed using an expert program that adjusts the dilution ratio at each step to meet the set objective. If the desired objective is to quantize a drug to 30^{th} level with probability of at least one atom or molecule in it, then the program either adds or subtracts the amount of alcohol, water or glucose to reach at the set goal. This is a form of computational optimization for drug quantization based on iterative simulation process. The simulation result for NLT model is shown in Figure 3.

Drug for homeopathic therapy can be standardized uniformly only by using NLT drug quantization model to a desired dilution level. Simulation result using NLT model to quantize three drugs to 30^{th} level for homeopathic pharmacy is shown in figure 4. This will definitely bring the low dilution therapy to scientific scrutiny. It will provide an ample opportunity to researchers either to verify the effectiveness of drug dilutions at nano-scale or declare them unfit for clinical practice compared to control studies such as placebo effects. The NLT drug quantization model will also help establish window for hormesis. This hormetic window for drugs will be very useful in designing treatment protocols. Most cancer cells eventually become resistant to MTD treatment protocols after some time. Once we know these hormetic drug ranges then it will be easy to avoid such resistant regions.

Our conventional drug doses are based on MTD that a patient can withstand during the course of chemotherapy. This methodology has severe side effects both on patient's general health and in combating the chronic diseases. MTD methodology eventually produces drug resistance viruses, bacteria and tumor cells after some time. A more pragmatic method is metronomic therapy in which small drug doses are administered regularly, frequently, and continuously for a long time to combat chronic diseases such as cancer.

A drug can be quantized to any desired level using NLT model. Suppose a tumor of known dimensions is the target of a drug. One can design and develop a drug for a treatment plan based on tumor information for individual patient. Given the drug's uptake percentage and the number of sensitive target cells one can calculate the drug strength to treat the disease. Cancer cells are usually in different phases such as Synthesis (S), Mitosis (M), G1 or G2. Only a fraction of cells

may be in the sensitive phase and a continuous administration of drugs in smaller doses for a longer time may be the solution to completely eradicate the disease.

The other target in tumor management is its endothelial vasculature, which unlike tumor cell cycle, is open to attack all the time. Even smaller drug doses are needed to effectively attack the angiogenesis to cure a tumor. Such smaller doses can also be quantized based on NLT model.

Example:

Consider a tumor with diameter, d, of 2 centimeters thickness. A typical tumor cell has a diameter, d', of 10 micron (μm). It is estimated that the total number of tumor cells in this volume are about 8 billion. If we need one drug molecule to kill single cancer cell then we need at least 8 billion drug molecules given all the other factors are kept at unity.

Let's consider how much dose is needed for the first layer of tumor cells given that the surface area of the solid tumor volume is given as $4\pi r^2$. Exposed area of the tumor cells is $\pi r'^2$ where r=1cm and r'=5 μm.

Number of tumor cells on surface exposed to drug molecules are = $(4x10^{-4})/(5x10^{-6})^2$ or 16 million cells on the top layer. This is about 0.2% of the total tumor cells in the total volume. Calculating dose for such top layer also involves other factors. Suppose 20% of these tumor cells are sensitive to a drug during the course of therapy. Assuming the drug uptake is 35% and the flow is 90% while all other factors are kept unity for simplicity, then the dose will be:

> Dose= (# of targets x sensitive cells)/(uptake ratio x fluid gradient x C_f) where C_f is the correction factor kept as unity.

The final dose = $(0.2x16x10^6)/(0.35x0.9x1.0)$=10.2 million drug molecules provided that single drug molecule is required to kill a single tumor cell. As this layer of tumor cells is removed the tumor will shrink and new dose will be modified based on new amount of exposed tumor cells. A simulation has been performed for different drugs to produce 4.3 million molecules in a dose for one successive layer. The results of drug quantization simulation are shown in Figure 5. Each drug has been quantized to a uniform level where each dose contains 4.3 million drug molecules.

Discussion and Conclusion

Our current medical technologies, both in diagnostic and therapeutic fields, have severe limitations. An x-ray, though noninvasive, cannot detect any mass smaller than 3 mm in diameter in our lungs [20]. No amount of x-ray, ultrasound or MRI can detect a hair in an eye yet one can

feel and see it. Similarly other diagnostic technologies are coarser and inefficient. A disease starts much earlier in a living organism than at the time it is detected with our current diagnostic tools. In our current medical practice a disease is left to grow to a level where it could be observed with our biomedical equipment. The drugs development and delivery system is equally poorer compared to the level of healthcare one can achieve through nanotechnology. Some potent drugs also cause severe side effects and over 100,000 patients die each year due to these problems in the USA alone.

Today, we can estimate the number of tumor cells in a tumor or the number of bacteria in an organ. If we need a single drug molecule to kill a bacteria or a tumor cell then we can also estimate the amount of drug needed to cure a disease. There may be instances when two or more than two drug molecules may be needed per target to effectively destroy a pathogen or a mutated cell. These are known as single target single hit, double target or multiple target models. Given this precision one can design treatment protocols for an individual patient. Similarly, body's reactive processes or immune system can be stimulated with much finer drug amounts than we are currently using in vaccination or immunization. This all is possible through nano-medicine where we will be able to develop and deliver drugs at atomic and molecular levels. Drugs at such scales will be safer, effective, inexpensive and more reliable.

The revolution of nano-medicine will be similar to or even greater than the impact of information technology in our society due to inexpensive computers and access to World Wide Webs. Highly effective but least toxic drugs would be available for chronic diseases, which will modify the medical practice in near future. The therapy for a disease will start much earlier based on objective and subjective symptoms compared to our present day mechanistic findings derived from diagnostic modalities. It may make our existing medical equipment either obsolete or limited to fewer procedures. Economic factor will be another incentive to adopt the nano-medicine. The practice of nano-medicine will force medical colleges to study emotions, symptoms, signals, systems, molecules and cells. Access to nano-drugs in the developing countries will bring the healthcare level at par with the developed countries for chronic diseases. All this will force us to redefine health, disease and drug concepts in the light of evolutionary biology and nano-technology. Health is not merely an absence of some annoying symptoms or a presence of some good feelings. A healthy state is one that can withstand the environmental changes and adapts to these evolutionary processes without overreacting or under acting to these

stimulus. Nano-drugs will help tune the biological systems to such demands. NLT models will form the corner stone of nano-scale drug processing methods to meet our health needs. The next step it to experimentally implement NLT models in a laboratory setting before manufacturing nano-scale drugs for routine clinical practice.

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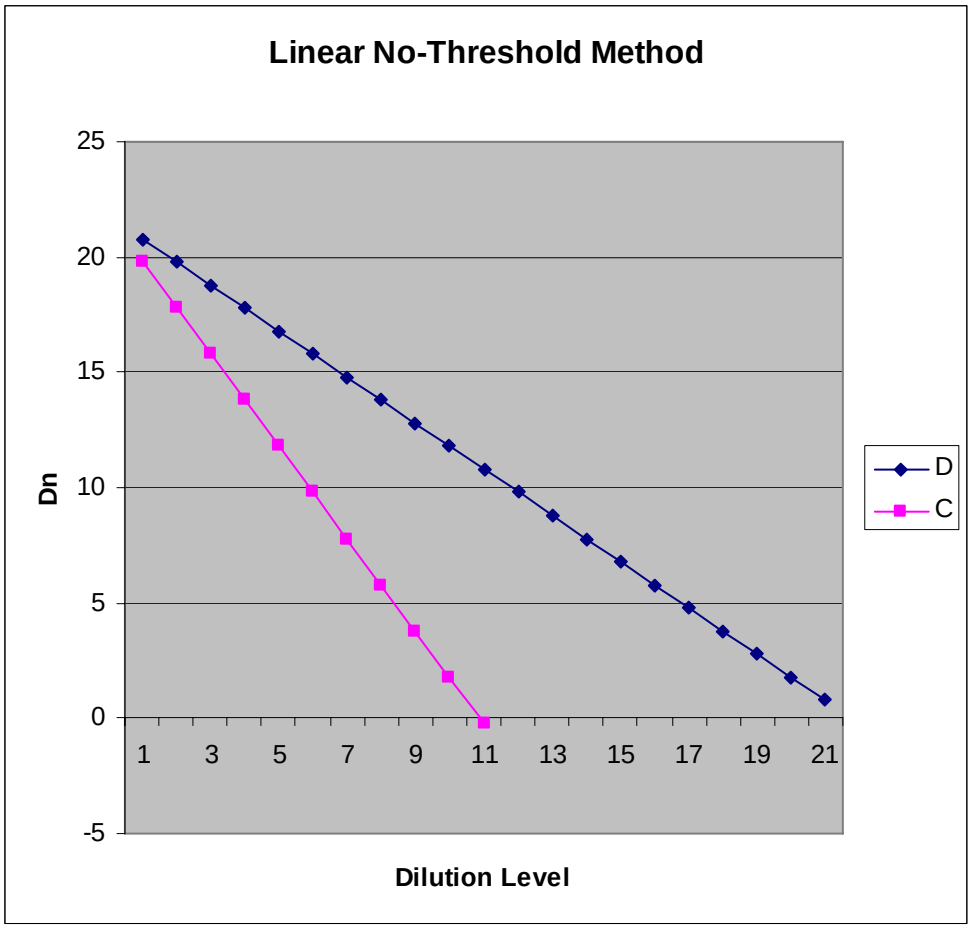

Figure1. Linear No Threshold model in which D is the decimal scale and C is the centesimal scale for diluting Arsenic Trioxide (As_2O_3) drug. D_n is the drug concentration probability at different dilution levels.

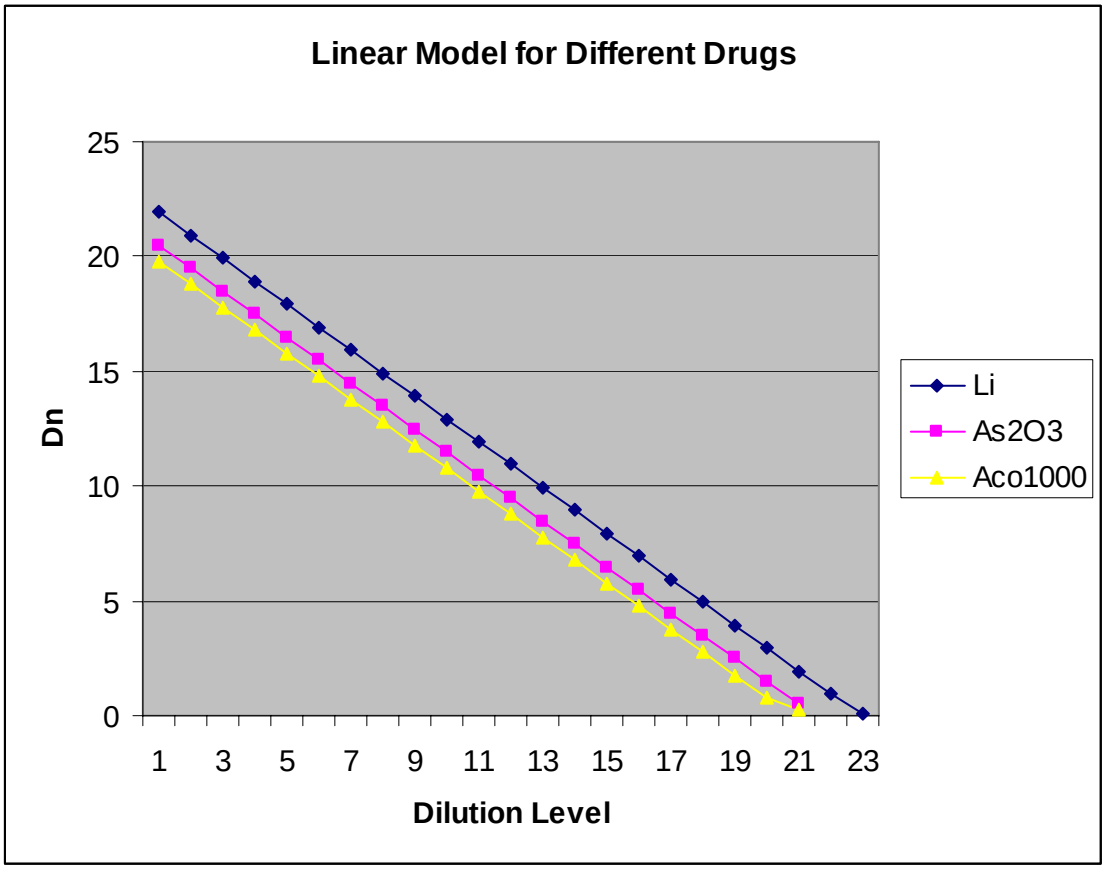

Figure 2: Three drugs, Lithium, As_2O_3, and Aco1000 cannot be standardized to a uniform scale because of their different atomic or molecular weights.

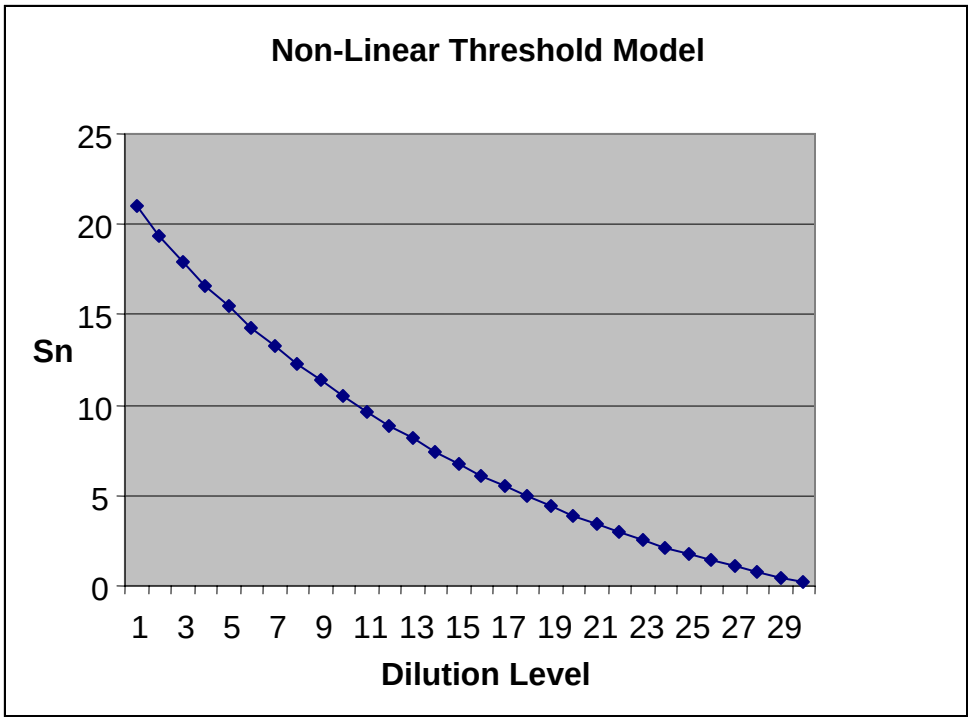

Figure 3: One gram of As_2O_3 can be quantized to a nano-scale at 30^{th} level using Non Linear Threshold model.

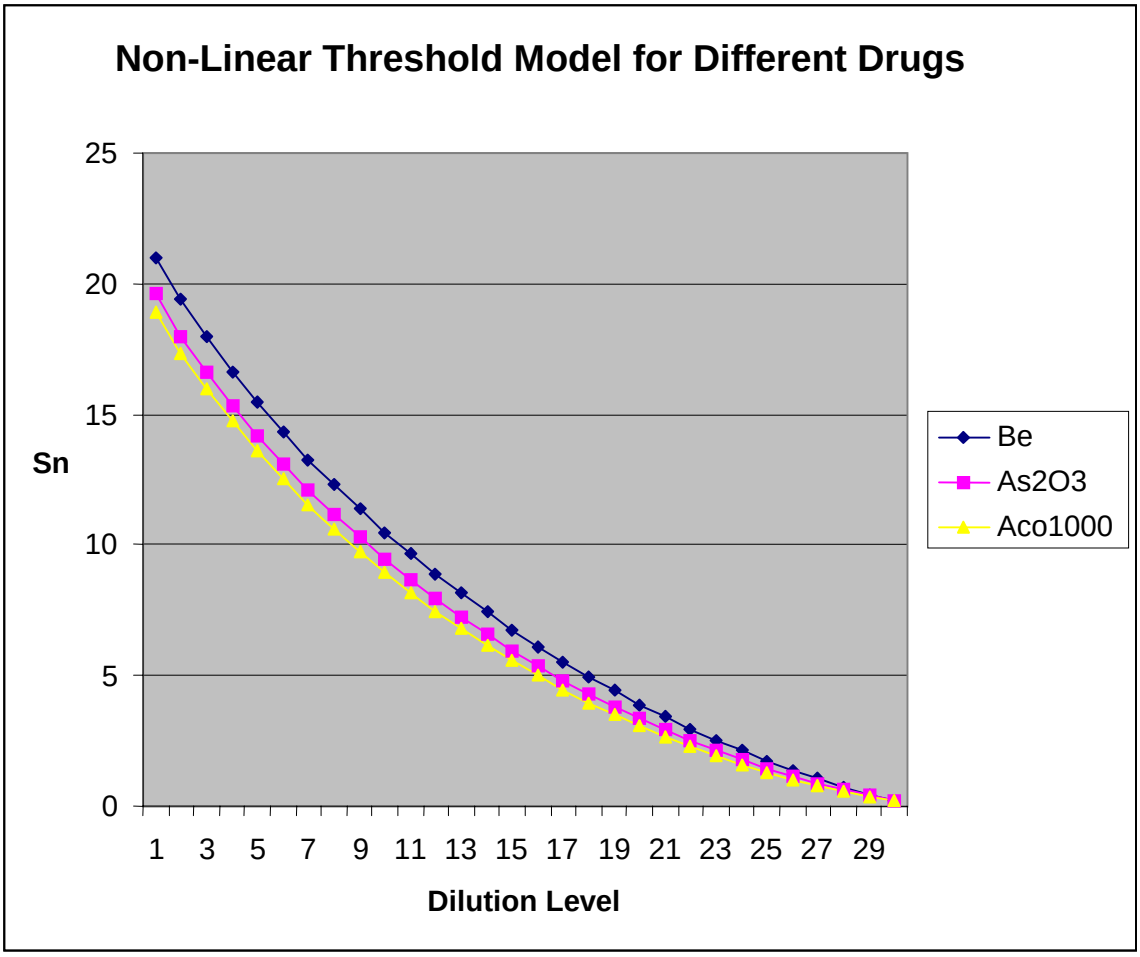

Figure 4: Three different drugs such as Be, As_2O_3, and Aco1000, starting with one gram each can uniformly be quantized to a unique 30^{th} scale using NLT model. S_n is the probability of drug concentration at different dilution levels.

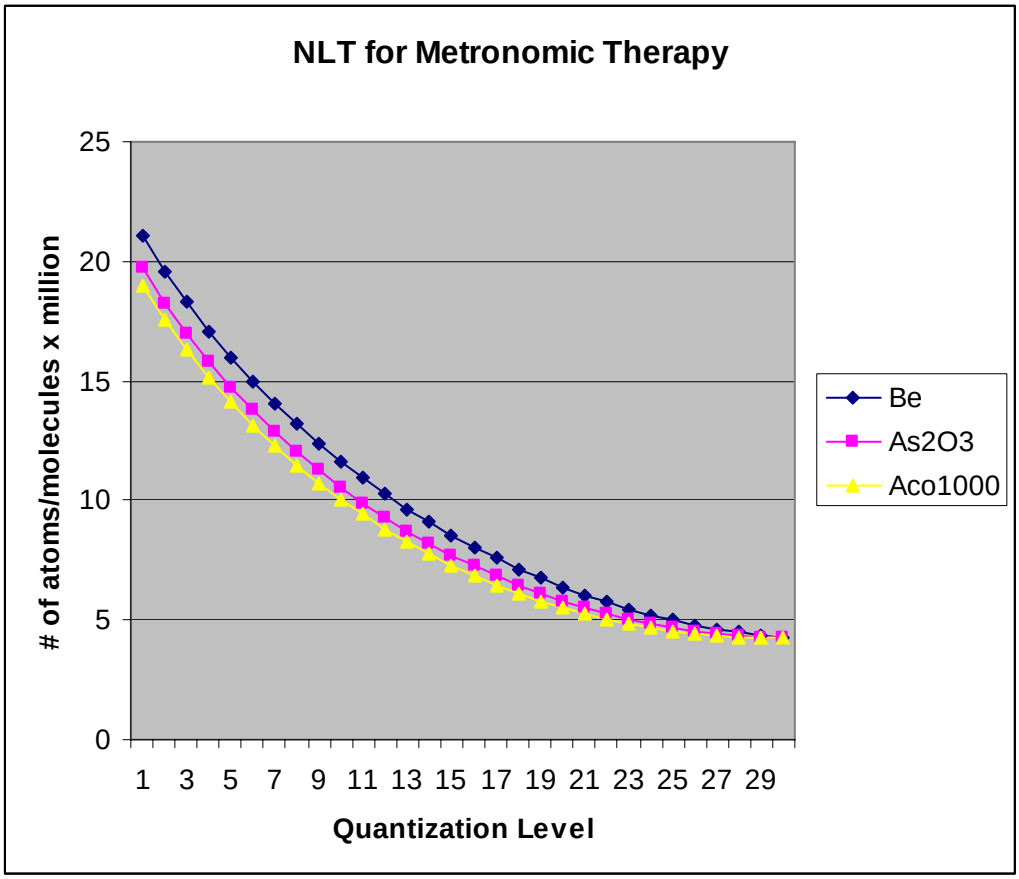

Figure 5: Drug quantization for metronomic therapy. Each drug dose contains 4.3 million drug atoms or molecules per dose. These doses of the drugs can be optimized based on individual case.