CRIMSON PUBLISHERS
Wings to the Research

Innovation in Tissue Engineering & Regenerative Medicine

Review Article

Applying Monte Carlo Method to Bioengineering: Decision Support System in Human Skin-Tissue Correlation

Nuno Domingues*

Department of Mechanical Engineering, Lisbon Superior Engineering Institute, Portugal

***Corresponding author:** Nuno Domingues, ISEL-ADEM, Email:nndomingues@gmail.com, Rua Conselheiro Emídio Navarro, Lisboa, Portugal

Submission: September 08, 2018; **Published:** September 18, 2018

Abstract

The skin is the biggest human organ and is subject to several submissions and aggressions. It is also one of the indicators of the beginning or on development diseases, such as tissue. Thereby, studying the tissues can be a boost to prevent major health impacts. However, being the biggest organ and having multiple characteristics that can differ along the body, the study can be time and resource consuming. This paper presents an algorithm that can be applied to prevent that the study of human tissue by skin deseases be jeopardize by the amount of data and analyses of skin.

Keywords: Decision support system; Bioengineering; Biomedical engineering; Mathematical modelling; Optimization; Computational systems; Algorithms; Tissue skin correlation

Introduction

Skin

The skin is the biggest human organ with a total area of about 20 square feet [1]. The skin protects us from microbes and the elements, helps regulate body temperature, and permits the sensations of touch, heat, and cold. Skin has three layers:

1. The epidermis, the outermost layer of skin, provides a waterproof barrier and creates our skin tone.

2. The dermis, beneath the epidermis, contains tough connective tissue, hair follicles, and sweat glands.

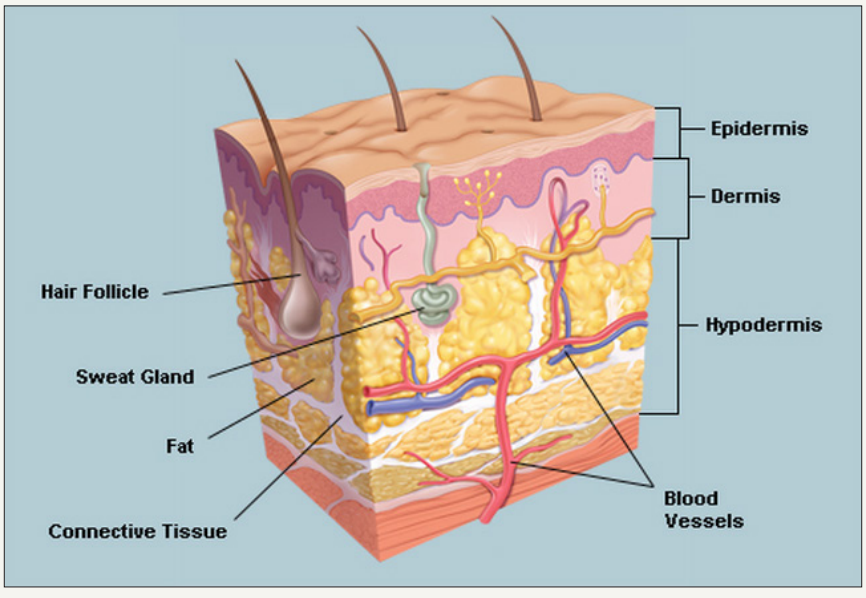

Figure 1: Skin layers.

The deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue. Figure 1 shows the layers of skin [2].

There are the following main skin conditions [2]:

1. Rash: Nearly any change in the skin's appearance can be called a rash. Most rashes are from simple skin irritation; others result from medical conditions.

2. Dermatitis: A general term for inflammation of the skin. Atopic dermatitis (a type of eczema) is the most common form.

3. Eczema: Skin inflammation (dermatitis) causing an itchy rash. Most often, it's due to an overactive immune system.

4. Psoriasis: An autoimmune condition that can cause a variety of skin rashes. Silver, scaly plaques on the skin are the most common form.

5. Dandruff: A scaly condition of the scalp may be caused by seborrheic dermatitis, psoriasis, or eczema.

6. Acne: The most common skin condition, acne affects over 85% of people at some time in life.

7. Cellulitis: Inflammation of the dermis and subcutaneous tissues, usually due to an infection. A red, warm, often painful skin rash generally results.

8. Skin abscess (boil or furuncle): A localized skin infection creates a collection of pus under the skin. Some abscesses must be opened and drained by a doctor to be cured.

9. Rosacea: A chronic skin condition causing a red rash on the face. Rosacea may look like acne and is poorly understood.

10. Warts: A virus infects the skin and causes the skin to grow excessively, creating a wart. Warts may be treated at home with chemicals, duct tape, or freezing, or removed by a physician.

11. Melanoma: The most dangerous type of skin cancer, melanoma results from sun damage and other causes. A skin biopsy can identify melanoma.

12. Basal cell carcinoma: The most common type of skin cancer. Basal cell carcinoma is less dangerous than melanoma because it grows and spreads more slowly.

13. Seborrheic keratosis: A benign, often itchy growth that appears like a "stuck-on" wart. Seborrheic keratoses may be removed by a physician, if bothersome.

14. Actinic keratosis: A crusty or scaly bump that forms on sun-exposed skin. Actinic keratoses can sometimes progress to cancer.

15. Squamous cell carcinoma: A common form of skin cancer, squamous cell carcinoma may begin as an ulcer that won't heal, or an abnormal growth. It usually develops in sun-exposed areas.

16. Herpes: The herpes viruses HSV-1 and HSV-2 can cause periodic blisters or skin irritation around the lips or the genitals.

17. Hives: Raised, red, itchy patches on the skin that arise suddenly. Hives usually result from an allergic reaction.

18. Tinea versicolor: A benign fungal skin infection creates pale areas of low pigmentation on the skin.

19. Viral exanthem: Many viral infections can cause a red rash affecting large areas of the skin. This is especially common in children.

20. Shingles (herpes zoster): Caused by the chickenpox virus, shingles is a painful rash on one side of the body. A new adult vaccine can prevent shingles in most people.

21. Scabies: Tiny mites that burrow into the skin cause scabies. An intensely itchy rash in the webs of fingers, wrists, elbows, and buttocks is typical of scabies.

22. Ringworm: A fungal skin infection (also called tinea). The characteristic rings it creates are not due to worms.

Connective tissue

Diseases of connective tissue include many different disorders that can affect skin, fat, muscle, joints, tendons, ligaments, bone, cartilage, and even the eye, blood, and blood vessels. Connective tissue holds the cells of our body together. It allows for tissue stretching followed by a return to its original tension (like a rubber band). It's made up of proteins, such as collagen and elastin. Blood elements, such as white blood cells and mast cells, are also included in its makeup [3].

There are several types of connective tissue disease. It's useful to think of two major categories. The first category includes those that are inherited, usually due to a single-gene defect called a mutation. The second category includes those where the connective tissue is the target of antibodies directed against it. This condition causes redness, swelling, and pain (also known as inflammation).

Connective tissue diseases due to single-gene defects cause a problem in the structure and strength of the connective tissue. Examples of these conditions include:

a. Ehlers-Danlos syndrome (EDS)

b. Epidermolysis bullosa (EB)

c. Marfan syndrome

d. Osteogenesis imperfecta

Connective tissue diseases characterized by inflammation of tissues are caused by antibodies (called autoantibodies) that the body incorrectly makes against its own tissues. These conditions are called autoimmune diseases. Included in this category are the following conditions, which are often handled by a medical specialist called a rheumatologist:

A. Polymyositis

B. Dermatomyositis

C. Rheumatoid arthritis (RA)

How to cite this article: Nuno D. Applying Monte Carlo Method to Bioengineering: Decision Support System in Human Skin-Tissue Correlation. Innovations Tissue Eng Regen Med. 1(2). ITERM.000506.2018.

D. Scleroderma

E. Sjogren's syndrome

F. Systemic lupus erythematosis

G. Vasculitis

People with diseases of connective tissue may have symptoms of more than one autoimmune disease. In these cases, doctors often refer to the diagnosis as mixed connective tissue disease [1].

Tissue-skin correlation

Tissue-skin correlation [4] identifies correlations based on laser measurements [5,6]. [7] presents the correlation of tissue constituents with the acoustic properties of skin and wound. [8] produces *in vivo* measurement of skin surface strain and sub-surface layer deformation induced by natural tissue stretching. [9] identifies the correlation between Nasal Microbiome Composition and Remote Purulent Skin and Soft Tissue Infections. [10] makes the comparison of Staphylococcus aureus from skin and soft-tissue infections in US emergency department patients. [11] analyses the national trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. [12] updates the information on community-acquired methicillin-resistant *Staphylococcus aureus* skin and soft tissue infection surveillance among active duty military personnel at Fort Benning GA. [13] studies the shifts in human skin and nares microbiota of healthy children and adults [14] highlights the hygiene strategies to prevent methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections, presenting a cluster-randomized controlled trial among high-risk military trainees. [15] produces practice guidelines for the diagnosis and management of skin and soft-tissue infections. [16] makes a Population Based Study of Seasonality of Skin and Soft Tissue Infections. [17] presents the study on increased US emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant *Staphylococcus aureus*. [18] reflects on emergence of community-acquired methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections as a common cause of hospitalization in united states children. [19] identifies the correlation of tissue constituents with the acoustic properties of skin and wound. [20] makes *in vivo* measurement of skin surface strain and sub-surface layer deformation induced by natural tissue stretching. [21] identifies a significant correlation between connective tissue growth factor gene expression and skin sclerosis in tissue sections from patients with systemic sclerosis.

Method

Existing models

There are some interdisciplinary approaches taking in consideration the normal structure/function of skin, exposure to clinical problems, diseases and more. This may include therapeutic Molecules and Cosmetics Testing, overall perspective on the clinical importance of skin models, clinical demands and diseased-skin in vitro models, organotypic and humanized animal models of Geno dermatoses, *In vitro* models, among others [3]. Other authors modelled the wounded skin [4] and others modelled both normal and wounded skins [5]. Whilst progress has been made to develop several alternative techniques to *in vivo* testing, further progress is required to reduce the dependency of toxicity testing on live animals. Now, in vitro methods cannot currently predict complex toxicological endpoints; however alternative testing methods could potentially reduce the number of animals used. [6] presents a review that demonstrates the versatility of biopolymers. It is still too early to speculate about the *in vivo* applicability of biopolymer-based scaffolds, due to the many unknowns regarding the biocompatibility of these scaffolds *in vivo*, as the immunological response and long-term stability of implanted biomaterials is still being studied. [6] What is common in the existing models is the amount of information needed to be analyzed and the expected time and effort consuming required to a dedicated and reliable model.

Monte Carlo method in a decision support system

Monte Carlo methods (or Monte Carlo experiments) are a broad class of computational algorithms that rely on repeated random sampling to obtain numerical results. Their essential idea is using randomness to solve problems that might be deterministic in principle. They are often used in physical and mathematical problems and are most useful when it is difficult or impossible to use other approaches [22]. Monte Carlo method can be applied to bioengineering in skin-tissue to generate draws from a probability distribution, modelling phenomena with significant uncertainty in inputs and simulating systems with many coupled degrees of freedom, such as cellular structures: Potts model, interacting particle systems, McKean-Vlasov processes. In principle, Monte Carlo methods can be used to solve any problem having a probabilistic interpretation. By the law of large numbers, integrals described by the expected value of some random variable can be approximated by taking the empirical mean (a.k.a. the sample mean) of independent samples of the variable. When the probability distribution of the variable is parametrized, mathematicians often use a Markov chain Monte Carlo (MCMC) sampler [23-26].

The central idea is to design a judicious Markov chain model with a prescribed stationary probability distribution. That is, in the limit, the samples being generated by the MCMC method will be samples from the desired (target) distribution [27]. By the ergodic theorem, the stationary distribution is approximated by the empirical measures of the random states of the MCMC sampler. In other problems, the objective is generating draws from a sequence of probability distributions satisfying a nonlinear evolution equation. These flows of probability distributions can always be interpreted as the distributions of the random states of a Markov process whose transition probabilities depend on the distributions of the current random states [28,29]. A natural way to simulate these sophisticated nonlinear Markov processes is to sample many copies of the process, replacing in the evolution equation the unknown distributions of the random states by the sampled empirical measures. [22] These models can also be the evolution of the law of the random states of a nonlinear Markov chain [30].

The Monte Carlo method developed here obeys to Little (1970) identified four criteria for designing models and systems to support management decisions:

a. Robust

b. Simple to control

c. Simple to understand

d. Complete (with interrelated and fundamental details).

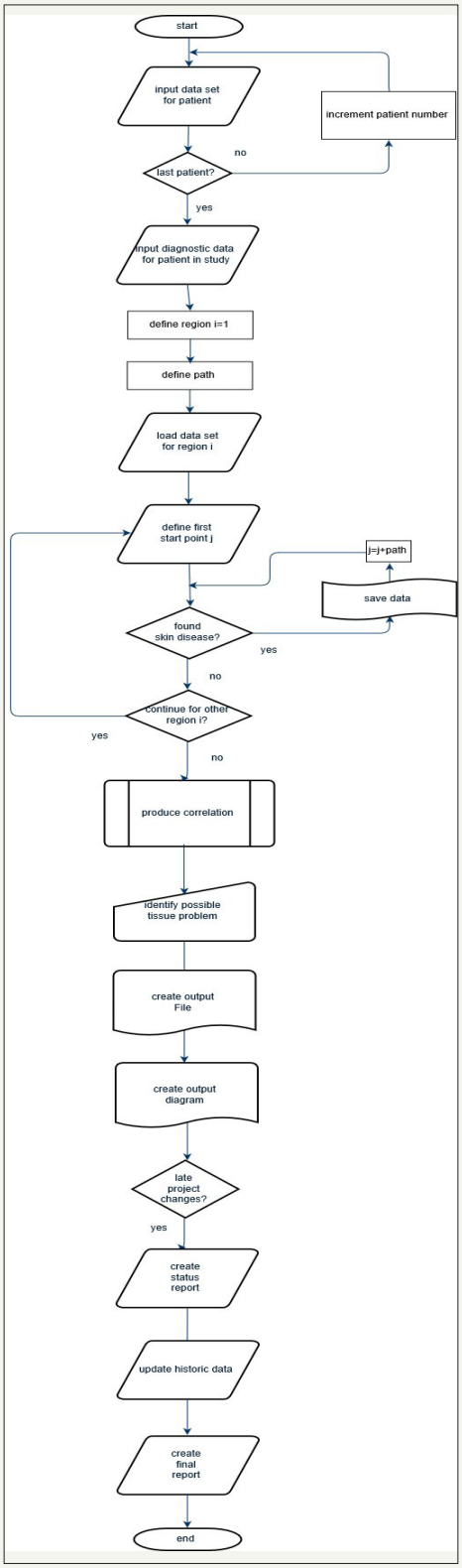

Figure 2: Method application fluxogram.

How to cite this article: Nuno D. Applying Monte Carlo Method to Bioengineering: Decision Support System in Human Skin-Tissue Correlation. Innovations Tissue Eng Regen Med. 1(2). ITERM.000506.2018.

Figure 2 presents the fluxogram of the proposed application method.

In the mid 80's the decision support systems (DSS) were divided into two areas:

a) Oriented to models: analysis based on a theory or a model, coupled with an interface that simplifies the use of the model;

b) Data-driven: intuitive models rely on historical data, involving simple calculations (such as averages, totals and statistical distributions) and storing of large amounts of data in formats that facilitate the decision making.

By this division, the present DSS is a hybrid because it uses both approaches. Using the user relationship criterion, it is defined a passive system, which helps the decision-making process, but does not offer explicit suggestions or solutions. Partially it can be considered as an active system because it can provide suggestions or solutions to the problem (the treatment when the patient has those clinical data). However, the last word is from the clinical expert that can look at the data produced just a guide and not as a dogma. Using the assistance criterion, the DSS is data-driven (manages, retrieves and manipulates unstructured information in a variety of formats storage), document-driven (focused on the retrieval and management of unstructured documents: oral, written, and video), knowledge-driven (expertise in problem solving through knowledge stored as facts, rules, procedures or similar structures), model-driven (using limited data and variables provided by the user and making statistical analysis, financial , optimization or simulation model) and trade-off-driven (possibly collaborative, involving trade-offs between different advantages and disadvantages, using the stored knowledge) [31,32].

The components of the DSS to be developed has the following segmentation [33-36]:

1. The data management system: where occur various activities related to recovery, storage and organization of data relevant to a particular decision

2. The model management system: performing recovery activities, storage and organization of the models that analytical support the DSS

3. The knowledge engine: where runs activities related to the recognition of the problem, and the generation of interim or final solutions. The engine of knowledge is the brain that brings together models and data and returns output able to assist in decision making

4. The user interface: It is the driver through which the user has access and can manipulate the entire system

5. The DSS user: the most important element of the components of DSS, because the whole system was designed to be under control and practice by the user.

The method starts by reading the historic data from previous patients. This data is a set of clinical, diagnosis, treatment, adjustments and response from patients. This data set also contains identified correlations skin-tissue disease, their range and their probability. Then it is read the patient data under supervision. The use of DSS is an interactive process modelling that has application in complex situations, under great uncertainty studies, the need for reasonable decision, the identification of alternatives, attempting to describe patterns, trends and correlations and to evaluate the relative importance of different alternatives with respect to multiple attributes, like quality and quantity.

The components (blocks) for the construction of a DSS model are the following [31-33]:

A. A quantitative criterion (or an objective) that the decision-maker is trying to maximize.

B. Variables

C. The variables that the decision-maker have the power to change directly

D. The variables that the decision-maker cannot control directly, and he doesn't know how it's going to turn out

E. The general variables ruled by a deterministic function it depends on.

F. Flows: a divided by time record that controls the inputs and the outputs. A flow may be unidirectional or bidirectional and needs a control variable.

G. Stocks, performing the function of storage, which can be four different types:

a. Reservoir: there is an inflow of water which mixes with the contents of the tank and increases the level of the reservoir. The outflow of water reduces the level of the reservoir. The reservoir is associated with the level measurement

b. Duct: collects what it is loading by keeping the order of entry and exit. This is a structure called a FIFO, but with a constant lag between input and output. Material arriving at time (t) leaves in (t + Δt). Operationally, the duct can simply cause a delay Δt between the input and output or can also changes the level

c. Queue: not common in DS, stores data in transit. Events such as arrivals and departures are discrete, while the times of attendance or how to stay in the lines are continuous

d. Lift: not common in DS. In this type, the elements wait in the queue, accumulate until a maximum number of elements and then get out (immediately or after a certain time)

H. Starting conditions: the values of the starting point of a study. A simulation can be extremely dependent on the initial status and values

Follows several random qualified samples of skin to investigate disease. When it is found, there are more samples collected nearby. In a decision problem, information only has value if, after receiving

the information, the decision-maker may improve and/or change its decision. On results, there are always two data elements to be look at by the clinical expert: the validity range and the value. The role of the DSS user is critical here, because there is need to interpret the solution, which can be [37]:

a) Single optimal: one-point maximizes the value for the objective function

b) Multiple solution: two or more points maximizes the value for the objective function

c) Degenerate: when the basic variable is zero

d) Infeasible: when no point satisfies all constraints. This means that the problem, the way it was formulated, has no solution

e) Unbounded: when the convex set that defines the feasible points is open in the direction of optimization.

Often the decision-maker deals with decisions with several objectives. Such situations are referred as decisions with multiple objectives, multiple criteria or multi attributes. In these situations, decisions often have a limited number of alternatives and desire to contemplate various goals, often contradictory. The first procedure implemented was called the lexicographer because the goals are ranked in order of importance with the same organization as a dictionary or a phone list. The lexicographic procedure is underprivileged because it minimizes the analysis of various objectives. Another procedure consists on the construction of a several entries matrix. The desired goals are order by importance, each intersection considered an alternative objective is flagged and the flags are added up in a column. The highest number defines the chosen goal and related decisions. This is a widely used simple method but has the limitation of not quantifying exchange compensations: a little more of a goal is much better than a little more on another. It is usually enhanced by the criteria of sufficiency: if an alternative does not include one of the goals listed as essential, this alternative is eliminated.

Expert knowledge is used instead of differential equations to describe a system, turning operations simpler. Thereby, all the data produced in each interaction is updated and new correlations are made at the end. This allows the method to learn as the diseases evolve [38].

Future Developments

The present paper describes theoretical how to develop a DSS using the Monte Carlo method applied to skin-tissue correlation. Authors with clinical data are encouraged to apply the present DSS to their own problems and patients.

There are several types of methods/models to be used by DSS. The most suitable for the scope of the present theme are:

a. Decision tree: a representation of a decision problem that displays the set of alternative values for each decision and probability variable as branches coming out of each node. The decision tree is simple to understand and shows a lot of details by possible paths or scenarios as sequences of branches from left to right

b. The influence diagram (ID) or closed loop diagram: also called a decision diagram or a decision network, a simple representation of a decision problem that offers an intuitive way to identify and display the essential elements, including decisions, uncertainties, objectives and how they influence each other. The influence diagram gives a high-level conceptual view on which the analyst may build a detailed quantitative model. ID was first developed in mid-1970s within the decision analysis community with an intuitive semantic that is easy to understand

c. What-if scenarios analysis: modifying variables (or relations between variables) to observe how the result changes

d. Sensitivity analysis: changing the value of only one variable, to observe the changes that this causes in other variables, estimating the value of some key variables

e. Demand analysis: rather than focus how variables influences and reacts, searches for sets of target values (a goal) for a variable. Then repeatedly changes other variables until reaching the target value

f. Optimization analysis: an extension of the demand for more complex objectives, seeking to find the optimum value for one or more target variables, within certain restrictions

g. Risk and uncertainty analysis: for example, Monte Carlo simulation, called like this after the famous casino in the Principality of Monaco on the French Riviera established in 1856. Monte Carlo simulation generates random numbers using a (pseudo) random number algorithm, representing the uncertainty by a probability distribution function.

Authors are encouraged to apply the basic principles of the present paper on developing other DSS, using the tools described above.

Conclusion and Reflections

The Monte Carlo method has several applications that can boost the investigation in bioengineering. The skin-tissue correlation is one of the fields that can be enhanced by turning a time and effort consuming task in a feasible and learning process. The method produces useful information that can identify possible diseases in an advance stage. The method also aids the clinical expert to decide the treatment.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

References

1. Diseases of Connective Tissue, from Genetic to Autoimmune, last access on 04th of September of 2018.

2. Hoffman M (2014) Picture of the Skin, last access on 04th of September of 2018.

3. Alexandra PM, Rogério PP, Mariana TC, Rui LR (2018) Skin tissue models. Elsevier ISBN 978-0-12-810545-0.

4. Egles C, Garlick JA, Shamis Y (2010) Three-dimensional human tissue models of wounded skin. Methods Mol Biol 585: 345-359.

5. Carlson MW, Alt Holland A, Egles C, Garlick JA (2008) Three-dimensional tissue models of normal and diseased skin. Curr Protoc Cell Biol 19: 19.9.

6. David C (2018) Skin Tissue Models. Scholar's Press, Germany.

7. Olerud EJ, D O'BrienJr, Henderson MAR, Steiger DL, Debel JR, et al. (1990) Correlation of tissue constituents with the acoustic properties of skin and wound. Ultrasound in Medicine & Biology 16(1): 55-64.

8. Maiti R, Gerhardt LC, Lee ZS, Byers RA, Woods D, et al. (2016) In vivo measurement of skin surface strain and sub-surface layer deformation induced by natural tissue stretching. Journal of the Mechanical Behavior of Biomedical Materials 62: 556-569.

9. Johnson RC, Ellis MW, Lanier JB, Schlett CD, Cui T, et al. (2015) Correlation between nasal microbiome composition and remote purulent skin and soft tissue infections. Bacterial Infections Journal 83(2): 802-811.

10. Talan DA, Krishnadasan A, Gorwitz RJ, Fosheim GE, Limbago B, et al. (2011) Comparison of Staphylococcus aureus from skin and soft-tissue infections in US emergency department patients, 2004 and 2008. Clin Infect Dis 53(2): 144-149.

11. Hersh AL, Chambers HF, Maselli JH, Gonzales R (2008) National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. Arch Intern Med 168(14): 1585-1591.

12. Leamer NK, Clemmons NS, Jordan NN, Pacha LA (2013) Update: community-acquired methicillin-resistant Staphylococcus aureus skin and soft tissue infection surveillance among active duty military personnel at Fort Benning GA, 2008-2010. Mil Med 178(8): 914-920.

13. Oh J, Conlan S, Polley EC, Segre JA, Kong HH (2012) Shifts in human skin and nares microbiota of healthy children and adults. Genome Med 4(10): 77.

14. Ellis MW, Schlett CD, Millar EV, Wilkins KJ, Crawford KB, et al. (2014) Hygiene strategies to prevent methicillin-resistant Staphylococcus aureus skin and soft-tissue infections: a cluster-randomized controlled trial among high-risk military trainees. Clin Infect Dis 58(11): 1540-1548.

15. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, et al. (2005) Infectious Diseases Society of America. 2005. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 41(10): 1373-1406.

16. Wang X, Sherry T, Sarada P, Chowell G (2013) A population based study of seasonality of skin and soft tissue infections: Implications for the Spread of CA-MRSA.

17. Pallin DJ, Egan DJ, Pelletier AJ, Espinola JA, Hooper DC, et al. (2008) Increased US emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant staphylococcus aureus. Ann Emerg Med 51(3): 291-298.

18. Frei CR, Makos BR, Daniels KR, Oramasionwu CU (2010) Emergence of community-acquired methicillin-resistant staphylococcus aureus skin and soft tissue infections as a common cause of hospitalization in united states children. J Pediatr Surg 45(10): 1967-1974.

19. Olerud JE, O'Brien WD, Henderson RMA, Steiger DL, Debel JR, et al. (1990) Correlation of tissue constituents with the acoustic properties of skin and wound. Ultrasound Med Biol 16(1): 55-64.

20. Maitia R, Gerhardt LC, Lee ZS, Byers RA, Woods D, et al. (2016) In vivo measurement of skin surface strain and sub-surface layer deformation induced by natural tissue stretching. Journal of the Mechanical Behavior of Biomedical Materials 62: 556-569.

21. Igarashi A, Nashiro K, Kikuchi K, Sato S, Ihn H, et al. (1995) Significant correlation between connective tissue growth factor gene expression and skin sclerosis in tissue sections from patients with systemic sclerosis. J Invest Dermatol 105(2): 280-284.

22. Monte Carlo algorithm last access on 04th of September of 2018.

23. Metropolis N, Rosenbluth AW, Rosenbluth MN, Teller AH, Teller E (1953) Equation of state calculations by fast computing machines. The Journal of Chemical Physics 21(6): 1087-1092.

24. Hastings WK (1970) Monte Carlo sampling methods using Markov chains and their applications. Biometrika 57(1): 97-109.

25. Liu JS, Liang F, Wong WH (2000) The multiple-try method and local optimization in metropolis sampling. Journal of the American Statistical Association 95 (449): 121-134.

26. Luca M, Jesse R (2013) On the flexibility of the design of multiple try Metropolis schemes. Computational Statistics 28(6): 2797-2823.

27. Spall JC (2003) Estimation via markov chain monte carlo. IEEE Control Systems Magazine 23(2): 34-45.

28. Vassili N (2010) Nonlinear markov processes. Cambridge Univ Press, UK, p. 375.

29. Del Moral, Pierre (2013) Mean field simulation for Monte Carlo integration. Monographs on Statistics & Applied Probability,

Chapman & Hall/CRC Press, USA, p. 626.

30. Del Moral P, Doucet A, Jasra A (2006) Sequential monte carlo samplers. (2015) Journal of the Royal Statistical Society 68 (3): 411-436.

31. MITT86, Mittra, Sitansu S (1986) Decision support systems tools and techniques, John Wiley & Sons, USA.

32. SPRA91, Sprague, Ralph H e Hugh J Watson (1991) Sistemas de Apoio à Decisão, Campus.

33. TOM 91, Tom Paul L (1991) Managing information as a corporate resource. Harper Collings Publishers, New York, USA.

34. (1998) Analytica User Guide, especially chapter 5: Building Effective Models and Chapter 6: Creating Lucid Influence Diagrams, from Lumina Decisions Systems.

35. (1996) Making hard decisions: an introduction to decision analysis (2nd edn), Duxbury Press, Belmont, CA, Australia.

36. Holtzman, Samuel (1989) Intelligent decision systems addison, Wesley, USA.

37. Pearl J (1988) Probabilistic reasoning in intelligent systems: Networks of Plausible Inference, San Mateo, CA: Morgan Kaufmann Publishers, USA.

38. Virine L, Trumper M (2008) Project decisions: The Art and Science, Vienna, VA: Management Concepts.