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Mathematical biology: a powerful science for progress

Abstract

This paper is about mathematical biology as a new fast growing and cooperative field of the two sciences: biology and mathematics. The challenge is thatmore quantitative becomes the biology science, wider and deeper becomes the application of mathematics in this science, hence more exciting results will be in the global scope. Many experiments in biology need quantification in order to make measurements, to discover and estimate the influence of different factors in the phenomenon under study, and draw right conclusions. An example is the estimation of the total number of choices a fly faces while travelling through the apparatus for fractionating the flies. The combinations of the successive choices result with a greatnumber. Comparative experiments estimate differences in response between treatments or between the two groups involved in the experiment. There are many cases where the comparisons are biased, no matter how precise the measurements are done, because of the way a group is partitioned into two subgroups. The biologist needs to know all the possible partitions and the respective numbers of comparisons, make them part of the experiment and find out which partition gives the lowest error. In this paper our intention is to help biologists and researchers with few formulas that can be used for calculations in different experiments.

Keywords: mathematical biology, quantitative measurements, genomic technologies, choices of travel, summation formulas, comparative experiments

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Introduction

Mathematical biology is a new fast growing and cooperative field of the two sciences,and the most exciting modern and competitive application of mathematics.

The more quantitative becomes the biology science wider and deeper becomes the application of mathematics in the science of biology, more fruitful will be the cooperation between the scientists and researchers of the two sciences, consequently, more exciting results will be internationally harvested.

"We mathematical biologists saw clearly that the enormous development of core mathematics and applied techniques in the twentieth century would find fruitful and important applications to biological systems."[1] Mathematical modelling offers new research tool and powerful laboratory technique to overcome the difficulties and the limitations that currently the biologists face. On the other side, there is a new challenge for mathematicians to intentionally study and understand the real and dynamic biology in order to promote the interdisciplinary involvement which is so essential for progress.…. " mathematical biology benefits all mathematicians; it is good for the health of mathematics as a whole."[1] "The application of mathematics in biology involves: making quantitative measurements, the collected biological data is used to develop mathematical models; hence approximate solutions of the models are obtained; the obtained solutions are used to make new predictions."[2] Mathematical modelling provides insight and it is very useful in summarizing, interpreting and drawing conclusions from the collected real data. Mathematics not only explains, but it also helps to solve a biological problem. We are not saying a complete solution because the modern biology needs to take further steps to construct comprehensive theories by promoting and realizing collaboration between biologists themselves, and between biologists and the scientists of the other sciences (particularly, of physics and chemistry). Everyone must keep in mind that collected data from a phenomenon can help to detect many factors and many functions, but the scientists barely can discover their cause, their interactions and theconsequences caused by them. "When we want to render phenomena from data, we often employ some kind of data-processing methods such as provided by statistical tools. However, we should be aware that these methods help detection, but not explanation.[3]

Therefore, implementing statistics in biology without understanding the scientificmethod actually misrepresents how science works.

Some current applications of mathematics in biology are:

Omics, which refers to a field of study in biology, is aiming at the collective characterization and quantification of pools of biological molecules that translate intothe structure, function and dynamics of organisms. Its target is the identification of allgene products present in a specific biological sample.

"X-omics" uses high technologies to acquire data on all X molecules and usingcomputational algorithms to infer causality from correlation.

"Modelling" constructs mathematical models of biological systems to become apredictive science like physics and engineering.

Molecular biology and the genomic technologies are facilitating rapid advances inunderstanding the molecular details of cells and the tissue function.

The increasing amount of genomic and molecular information is the basis for understanding higher-order biological systems, such as the cell and the organism,and their interactions with the environment, as well as for medical, industrial and other practical applications.[4]

"Mathematical biology is a fast-growing, well-recognised, albeit not clearly defined…, it is required to bridge the gap between the level on which most of our knowledgeis accumulating (in developmental biology it is cellular and below) and the macroscopic level of the patterns we see."[5] Advances in high experimental technologies have generated massive amounts of data on bio-molecular networks. To deal with the complexity of these networks, systematic methods are clearly required in order to derive meaningful information from their structure. The complexity of these networks in cellular biology and the mechanisms used, related to them, presents numerous challenges and difficulties tothe network researcher, hence the network researcher needs full knowledge of mathematical concepts, models, structures and algorithms. The mathematical discipline which underpins the study of complex networks in Biology and elsewhere is graph theory.[6]

Following the enormous advances in molecular biology it is now possible to study cellular processes not only at the level of a whole cell, but at the level of their network as well. Molecular networks, such as protein interaction [7,8,9], metabolic[10] and gene regulation networks[11,12] aim to capture such sets of biological processes in a single and coherent framework. In reality, all these different networks are connected and interwoven inside a cell; protein productsinteract with each other, regulate the expression of genes as well as digesting nutrients and catalyzing basic biochemical reactions in a cell's metabolism.

When we want to render phenomena from data, we often employ some kind of data-processing methods such as provided by statistical tools. However, we should be aware that these methods help detection, but not explanation.[3] Therefore, implementing statistics in biology courses without understanding the scientific method actually misrepresents how science works.

Application of mathematics in geotaxis

Geotaxis relates to the effects of gravity on animals and insects behaviour. For example, some fruit flies respond to gravity by choosing to fly into either high or low level tubes when given choices in glass mazes. A geotactic response is a movementin response to gravity. General body orientation to light (phototaxis) and gravity is orientation behaviour without movement. Many organisms have the ability to use theearth's magnetic field for navigation and orientation. Such is drosophila melanogaster, and is reported that negative geotaxis in flies, scored as climbing, is disrupted by a static electromagnetic field (EMF) and this is mediated by cryptochrome (CRY)-the blue light.[13]

The tree of life includes an extraordinary diversity of animal behaviour: foraging, reproducing, moving through the environment, and avoiding predators. These are the major determinants of survival and reproductive success and is thought to be under relatively strong natural and sexual selection.[14] In recent decades, a number of natural genetic polymorphisms that affect behaviourhave been identified, and some progress has been made toward understanding howchanges in DNA alter gene expression and/or protein structure, nervous system development, and neural physiology to produce differences in behavior.[15,16,17,18]

Selection experiments and experimental evolution approaches offer powerful tools for elucidating the origin and mechanisms of behavioural diversity. The discipline isuseful to establish basic knowledge about nature, but it also has powerful applications for biomedicine.[14]

Behaviour is highly sensitive to small and often uncontrollable environmentalinfluences, as well as the animal's physiological and motivational states.

For example, the response of parasitoid wasps to plant volatile chemicals is stronglyaffected by atmospheric pressure.[19] Furthermore, behaviour ofmost animals may be influenced by the memory of past experience. In artificial selection, a target behaviour is quantified for a number of individuals, and some top or bottom fraction is selected as breeders to produce the next generation.[20] Artificial selection is a powerful tool to explore the question of how behaviour evolves (i.e., the underlying proximate mechanisms), but it is less informative concerning the adaptive significance (i.e., costs and benefits) of behaviour.[14]

Mass selection, relies on an experimental setup that sorts individuals into groups depending on a particular behaviour. An example of mass selection is testing odourpreference which can be applied by running large numbers of individuals through a Y-maze with the focal odour coming from one arm and another odour from the otherarm, and breeding the next generation from those that chose the arm with the focal odour. This approach allows for greater population sizes, thus alleviating the problemof inbreeding. But the selection imposed this way will be rather weak because the distribution of the underlying preference trait remains unknown, so the differentiated selection cannot be estimated. In probably the longest experimental evolution study on behaviour in a eukaryote, *Drosophila* were selected for over five hundred generations for geotaxis, using a simple but ingenious setup that sorted flies according to their geotaxis score on the scale from 1 to 9 (Figure 1). Unfortunately, not all behaviours are amenable (controlled) to such automatic sorting.[14]

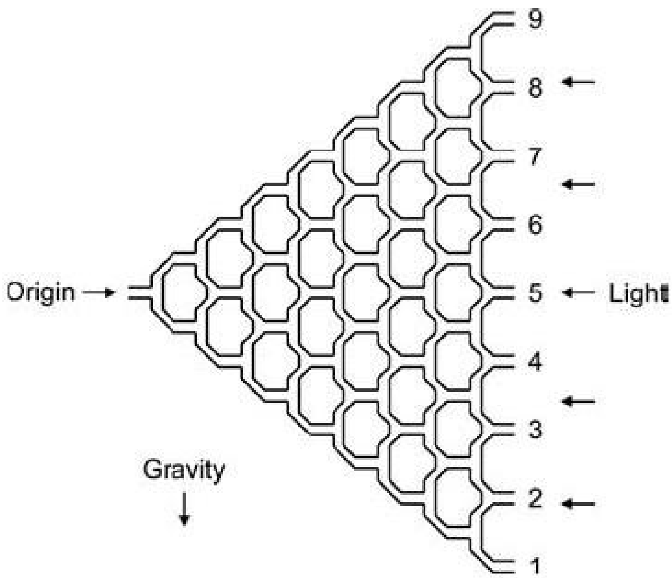

Figure 1 Theodore and Michael.[14]

***The behaviours are very difficult to control because there is a great number of choices a fly has to choose when they move from the origin to the end where is trapped. Look at the figure below: flies are released at the origin and move to the right, attracted by light, having to choose at each fork whether they move up or down. Let calculate, just for one fly, the total number of choices to move at all the stages consisted of the forks of the apparatus for fractionating the flies. At the entrance (origin) there is one choice for moving for a fly, just fly into the Y-maze apparatus. After it, the fly faces two paths created by the first fork. The combinationsof the first choice with these two choices produce 1 x 2 choices of movement. After the 2 paths the fly has to take decision which one of the 3 paths, created by 2 forks, in front of which it is found, it has to move. At this stage, the fly has 3 options. The combination of the previous 2 paths with these 3 new paths produces 2 x 3 choices.Then we have the following stage, where the fly is found at the front of 4 paths, created by 3 forks. So, there are 4 options it can move further to the right. The combined choices, at this stage, produce 3 x 4 alternatives. The same way are calculated the combined alternatives for the next stages, up to the end.

Consequently, the total of all the combined choices is consisted of the sum ofcombined choices at each stage. That is,

1 x 2 + 2 x 3 + 3 x 4 + 4 x 5 + ……….

The apparatus for fractionating flies according to geotaxis used in the five-hundred- generation mass selection experiment of Hirsch and coworkers.[21,22] The flies are released at the origin and move to the right attracted by light, having to choose at each fork whether they move up or down. Traps at the end collect flies according to their geotaxis score, from 1 (strong positive geotaxis) to9 (strong negative geotaxis). The result, above, relates just to the combined choices of one fly. But how many flies are released at the origin?! Such number corresponds to each fly.

*** Now, the task is to calculate the above sum. It is important to make such calculations for the biologist and researcher in order to carry out the experiment by making corrections, by looking back at the previous stages, by modifying parts of theexperiment etc., in order to draw right conclusions. It is not easy to sum up such successive products when there is a great number of them. Not to spend excessive time in calculations, better is to use summation formula. Following, are steps to find a proper formula.

Start with formula

$(n-(n-1))^2 = n^2 - 2\cdot n\cdot(n-1) + (n-1)^2$

Applying it for $n = 1, 2, 3, \ldots, n$ get:

$(1-0)^2 = 1^2 - 2\cdot 1\cdot 0 + 0^2$

$(2-1)^2 = 2^2 - 2\cdot 2\cdot 1 + 1^2$

$(3-2)^2 = 3^2 - 2\cdot 3\cdot 2 + 2^2$

……………………………………..

$(n-(n-1))^2 = n^2 - 2\cdot n\cdot(n-1) + (n-1)^2$

Summation side by side leads to the following result:

$1 + 1 \ldots .+1 = 1^2 + 2^2 + \cdots + n^2 - (2\cdot 1\cdot 0 + 2\cdot 2\cdot 1 + 2\cdot 3\cdot 2 \ldots + 2\cdot n\cdot(n-1))$

$+ 0^2 + 1^2 + 2^2 + \cdots + (n-1)^2$

$2\cdot 2\cdot 1 + 2\cdot 3\cdot 2 \ldots + 2\cdot n\cdot(n-1) = 2\cdot(1^2 + 2^2 + \cdots + n^2) - n^2 - n$

Known that,

We get,

$$1^2 + 2^2 + \cdots + n^2 = \frac{n(n+1)(2n+1)}{6}$$

$$2\cdot[1\cdot 2 + 2\cdot 3 + 3\cdot 4 + \cdots + (n-1)\cdot n] = 2\cdot\frac{n(n+1)(2n+1)}{6} - n^2 - n$$

$$2\cdot[1\cdot 2 + 2\cdot 3 + 3\cdot 4 + \cdots + (n-1)\cdot n] = \frac{n(n+1)(2n+1)}{6} - n\cdot(n+1)$$

$$= \frac{2n}{3}\cdot(n^2-1)$$

Definitely,

$$1\cdot 2 + 2\cdot 3 + 3\cdot 4 + \cdots + (n-1)\cdot n = \frac{(n-1)\cdot n\cdot(n+1)}{3}$$

Note: the second factor of the last summand at the left side is the factor in themiddle of the nominator at the right side.

In the above experiment where *Drosophila* were selected for over five hundred generations for geotaxis, using a simple setup that sorted flies according to theirgeotaxis score on the scale from 1 to 9, the total number of combined choices is:

$$1\cdot 2 + 2\cdot 3 + 3\cdot 4 + \cdots + 8\cdot 9 = \frac{8\cdot 9\cdot 10}{3} = 240$$

We draw the attention here that, if we wanted to calculate the number of paths travelled by the fly from origin to the end, that number is much greater. That number is:

9! = 1 x 2 x 3 x ….x 9 >> 240

Determining the effect of partitioning in a comparative experiment

To design an experiment there are many possibilities that relate to test and comparevarious combinations of soil and plants, or seeds, or animals, or patients to observe the plant growth, or the differences between the organisms living in different conditions. Plant growth comparisons are affected by several factors such as seed variety, amount of water, soil type, amount of light, temperature, humidity and other, but, also, by the way the experimental group is divided or partitioned. The purpose ofan experiment might be the observation of differences between the plants grown in different soils, or between patients as they live in different conditions, or related to the way they are divided into subgroups. As a rule, treatment plots must be arranged randomly, also the patients or animals must be randomly chosen. Comparisons are done one by one, and the number of comparisons depend on the number of partitions done within the group of the seeds or plants or patients, assigned for the experiment.

Studies of smoking and human health are observational, but the link that they have established is one of the most important public health issues today. Similarly, observational studies have established an association between heart valve disease and the diet drug fen-phen that led to the withdrawal of the drugs fenfluramine and dexfenfluramine from the market.[23]

The experiment must be in control and consistent in order to achieve responsiveness. Consistency means that, all other things being equal, the relationship between two variables is consistent across populations in direction and maybe in amount. Responsiveness means that we can go into a system, change thecausal variable, and watch the response variable change accordingly. Experiments can demonstrate consistency and responsiveness. Thus, if we see a consistent difference in observed response between the various treatments, we can infer that the treatments caused the differences in response.[24]

Comparative experiments estimate differences in response between treatments or between the two groups involved in the experiment. If the experiment has systematic error, then the comparisons will be biased, no matter how precise the measurements are done. To reduce the systematic error, the experimenter needs to observe and analyze different ways of partitioning an experimental group into two subgroups, and find out which one gives the lowest error.

Suppose we have a group of 10 plants, 10 seeds or 10 patients that will be submitted to an experiment to compare two types of soils, two types of drugs, two types of living conditions and so on. The group of ten elements must be divided into two subgroups where one subgroup will be planted in one type of soil and the other subgroup in the other type, one subgroup will experience one type of condition and the other subgroup experience the other type (similarly, one group take one drug and the other one a different one and so on). To find out which partition gives the lowest error during the comparative observations, the experimenter needs to observe and analyse different ways of partitioning the experimental group into two subgroups: 1 versus 9, 2 versus 8, 3 versus 7 etc. After arranging and experimenting all the possible partitions of this type the experimenter can draw the right inferences.

Following we consider the different ways of partitioning and the number of partitions into two subgroups.

Auxiliary formula

Sum of the squares of the first consecutive odd natural numbers Known that,

$$1^2 + 2^2 + \cdots + n^2 = \frac{n(n+1)(2n+1)}{6}$$

Apply this formula for the first consecutive $2 \cdot n$ numbers.

$$1^2 + 2^2 + \cdots + (2 \cdot n)^2 = \frac{2 \cdot n(2 \cdot n+1)(4 \cdot n+1)}{6}$$

Separate the sum of the squares into two classes,

$$[1^2 + 3^2 + \cdots + (2 \cdot n-1)^2] + [2^2 + 4^2 + \cdots + (2 \cdot n)^2] = \frac{n(2 \cdot n+1)(4 \cdot n+1)}{3}$$

$$[1^2 + 3^2 + \cdots + (2 \cdot n-1)^2] + 4 \cdot [1^2 + 2^2 + \cdots + (n)^2] = \frac{n(2 \cdot n+1)(4 \cdot n+1)}{3}$$

$$[1^2 + 3^2 + \cdots + (2 \cdot n-1)^2] + 4 \cdot \frac{n(n+1)(2n+1)}{6} = \frac{n(2 \cdot n+1)(4 \cdot n+1)}{3}$$

Hence,

$$1^2 + 3^2 + \cdots + (2 \cdot n-1)^2 = \frac{n(2 \cdot n+1)(4 \cdot n+1)}{3} - 2 \cdot \frac{n(n+1)(2n+1)}{3}$$

Thus way, the sum of the squares of the first consecutive odd natural numbers is:

$$1^2 + 3^2 + \cdots + (2 \cdot n-1)^2 = \frac{n(2 \cdot n-1)(2 \cdot n+1)}{3}$$

Now, use the consecutive formulas;

$$(1-n)^2 = 1^2 - 2 \cdot 1 \cdot n + n^2$$

$$(2-(n-1))^2 = 2^2 - 2 \cdot 2 \cdot (n-1) + (n-1)^2$$

$$(3-(n-2))^2 = 3^2 - 2 \cdot 3 \cdot (n-2) + (n-2)^2$$

$$\cdots\cdots\cdots$$

$$(n-1)^2 = n^2 - 2 \cdot n \cdot 1 + 1^2$$

The system of these equations can be written,

$$(1-n)^2 = 1^2 - 2 \cdot 1 \cdot n + n^2$$

$$(3-n)^2 = 2^2 - 2 \cdot 2 \cdot (n-1) + (n-1)^2$$

$$(5-n)^2 = 3^2 - 2 \cdot 3 \cdot (n-2) + (n-2)^2$$

$$\cdots\cdots\cdots$$

$$((2\,\mathrm{n}-1)-n)^2 = n^2 - 2 \cdot n \cdot 1 + 1^2$$

Expanding the left sides we get,

$$1^2 - 2 \cdot 1 \cdot n + n^2 = 1^2 - 2 \cdot 1 \cdot n + n^2$$

$$3^2 - 2 \cdot 3 \cdot n + n^2 = 2^2 - 2 \cdot 2 \cdot (n-1) + (n-1)^2$$

$$5^2 - 2 \cdot 5 \cdot n + n^2 = 3^2 - 2 \cdot 3 \cdot (n-2) + (n-2)^2$$

$$\cdots\cdots\cdots$$

$(2n-1)^2 - 2 \cdot (2n-1) \cdot n + n^2 = n^2 - 2 \cdot n \cdot 1 + 1^2$ Summing up side by side is got,

$$[1^2 + 3^2 + \cdots + (2 \cdot n-1)^2] - (2 \cdot 1 \cdot n + 2 \cdot 3 \cdot n + 2 \cdot 5 \cdot n + \cdots + 2 \cdot (2\,\mathrm{n}-1) \cdot \mathrm{n}) + \mathrm{n}^3 =$$

$$(1^2 + 2^2 + \cdots + n^2] - 2 \cdot [1 \cdot n + 2 \cdot (n-1) + 3 \cdot (n-2) + \cdots + n \cdot 1] +$$

$$\mathrm{n}^2 + (\mathrm{n}-1)^2 + (n-2)^2 + \cdots 2^2 + 1^2$$

Hence,

$$2 \cdot [1 \cdot \mathrm{n} + 2 \cdot (\mathrm{n}-1) + 3 \cdot (n-2) + \cdots + n \cdot 1] = 2 \cdot (1^2 + 2^2 + \cdots + n^2) -$$

$$[1^2 + 3^2 + \cdots + (2 \cdot n-1)^2] + 2n(1 + 3 + \cdots + (2n-1)) - \mathrm{n}^3$$

Replacing the above formulas we get,

$$2 \cdot [1 \cdot n + 2 \cdot (n-1) + 3 \cdot (n-2) + \cdots + n \cdot 1] =$$

$$= 2 \cdot \frac{n(n+1)(2n+1)}{6} - \frac{n(2 \cdot n-1)(2 \cdot n+1)}{3} + 2 \cdot n \frac{1 + 2 \cdot n - 1}{2} \cdot n - n^3$$

$$2 \cdot [1 \cdot n + 2 \cdot (n-1) + 3 \cdot (n-2) + \cdots + n \cdot 1] = \frac{n(2n+1)}{3} . (n + 1 - 2 \cdot n + 1) + n^3$$

Definitely,

$$1 \cdot n + 2 \cdot (n-1) + 3 \cdot (n-2) + \cdots + n \cdot 1 = \frac{n \cdot (n+1) \cdot (n+2)}{6}$$

Turning back to the group of 10 plants, 10 seeds or 10 patients that will be involvedin an experiment to compare two types of soils/drugs/living conditions and so on, letcalculate the number of ways the group of ten is divided and the number of comparisons between elements of the two groups in each case. To find out which partition gives the lowest error during the comparative observations, the experimenter needs to observe and analyse different ways of partitioning the experimental group into two subgroups: 1 versus 9, 2 versus 8, 3 versus 7 etc

The first group has 1 element and the other 9 (1 versus 9) . There are 1 x 9comparisons between the elements of the two groups.

The first group has 2 elements and the other 8 (2 versus 8). There are 2 x 8comparisons between the elements of the two groups.

The first group has 3 elements and the other 7 (3 versus 7). There are 3 x 7comparisons between the elements of the two groups.

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In total, there are $1 \times 9 + 2 \times 8 + 3 \times 7 + \ldots + 9 \times 1 = \frac{9 \cdot 10 \cdot 11}{6} =$ 165 comparisons.

Conclusion

The summation formulas, presented in this paper, are very useful for a researcher because they facilitate very much the tedious work for calculation, not only for biologists and mathematicians but for researchers and scientists of other fields such as chemistry, physics, genetics, sociology, psychology etc. It is a matter of the researchers and scientists of the respective field to study and reveal where and how they can be used. There is no doubt with regard to their use in comparative experiments. As mentioned in abstract, generally, the comparisons are biased because of the way a group is partitioned into two subgroups or more. In order to avoid this problem, the biologists need to know all the possible partitions and the respective numbers of comparisons, make them part of the experiment and find out which partition gives the lowest error. In order to draw right conclusions, biologists and researchers carry out an experiment by using different mathematical formulas, by making corrections, by looking back at the previous stages, by modifying parts of the experiment etc... We note here that, to spend not excessive time in calculations, the better choice is to use summation formula. We think that the above formulas will be a great help for biologists and researchers of other fields for calculations in different experiments. We welcome every remark regarding these summation formulas, and especially new proposals or suggestions as to their use in relation withthe fields discussed in this paper, or other fields.

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Conflicts of interest

The authors declared no have conflict interest for the study.

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