Resonance and Anti-Resonance: From Mathematical Theory to Clinical Cancer Treatment Design

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"We unfortunately learned the slow way that intuitive trial and error combination of drugs—without any quantitative guidance as to the influence of each manipulation on end results is apt to result in no improvement, only discouragement and little useful information for future planning" (Skipper,1986).

Abstract

Models of population dynamics, under various distributions of environmentally-inflicted loss processes, suggest that population persistence depends on the level of synchronization of the environmental and population processes. Population growth is maximized when disturbance periodicity is an integer or fractional multiple of the population characteristic periodicity. This Resonance Phenomenon is observed in as diverse models as those of mussels in the intertidal zone under harsh weather regimes, those of humans exposed to pulsed measles

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vaccination policies and those of cancer and host cell populations under periodic chemotherapy. In each case resonances result from some specific properties of the system at hand, thus suggesting the universality of this phenomenon. A large variance in the intrinsic biological periodicity damps-down the resonance effect and a similar "Anti-Resonance" effect is created by random drug pulsing. Based on model analysis it was suggested that chemotherapy by cell-cycle phase-specific drugs can be optimized by schedules, employing the Resonance/Anti-Resonance effect in conjunction with known differences in cell-cycle distributions of host and cancer cells. This method, termed *Z-Method*, was verified both *in vitro* and *in vivo*. For tuning-up the method to clinical needs a new heuristic optimization method was developed, complying with complex criteria for treatment efficacy and the mathematical models of both pathology and physiology were upgraded to fit the Non-Hodgkin Lymphoma disease (NHL) and thrombocytopenia. Quantitative predictions about the optimal administration of the chemotherapy supportive drug, TPO, were validated in preclinical trials and it was suggested that the developed models and their validation procedures provide solid grounds for further employment of biomathematics in medicine.

1 INTRODUCTION

Why has so little progress been made in the last three decades of war against cancer? While there have been substantial achievements in this field, the overall result of this war, launched by the USA government in 1971, is more than 73% increase in USA annual cancer death toll over the last thirty years. One of the major reasons for that is investigators' reliance on animal models, which are consistently bad in predicting treatment success. Moreover, today, researchers invest most of their efforts in the study of intracellular drug effects, but altogether ignore the effects on the body of the patient as a whole (Clifton Leaf, Fortune Magazine, March 2004).

In the 1980's there was a consensus in the biomedical research community that cancer progresses hazardously and, hence, does not yield to prediction at any level of accuracy. In general, it was believed that biological systems are too complex to be accurately retrieved by mathematical models. This declarable mistrust in the power of biomathematics left the biomedical sciences lagging behind

other sciences, as an immature sequel of experimental observations.

During the same years, bio-mathematicians constructed various models for nonlinear population dynamics in diverse environments. Among those was the Resonance Theory of population persistence in randomly fluctuating environments, which was later applied to cancer chemotherapy. This theory, its various implementation in oncology, and its prospective validation in the pre-clinical setting, is the subject-matter of the present review.

The most important premise, underlying the application of the Resonance Theory in oncology, is that biology and medicine obey universal laws, as classical sciences do, and that these laws should be applicable at all levels of biological organization. Therefore, it can be expected that the laws that are shown to operate on one organization level of the biological system also describe the behavior of the system on other levels of organization. Thus, infererence from the laws governing the dynamics on the populations level of whole organisms can aid in understanding the dynamics of intra-organismic physiological and pathological processes [5]. The resulting theory, once validated experimentally, can help in substantiating biology as a mature science.

The current review is ultimately aimed at illustrating how the paradigm of medical treatment can be changed: from the prevalent, trial-and-error paradigm into a new paradigm of prediction-based decision-making in the choice of treatment schedules. This possible transition will be illustrated by briefly relating the Resonance Theory, its various applications, most notably in cancer chemotherapy, the biomedical validation of the theory in cancer and the implications for cancer therapy. We will underline significant milestones in the development of the concept: (i) problem-focused simple models; (ii) universal theories applicable to different biological organization levels; (iii) testable treatment optimization concepts; (iv) experiments to test theories; (v) quantitatively accurate models; (vi) preclinical and clinical validation.

2 THE RESONANCE PHENOMENON IN POPULATION DYNAMICS

In the early 1980's it was recognized that different models of population dynamics, in environments that are characterized by alternating episodes of disturbance and favorable conditions, have a common conceptual basis: if the environmental conditions exhibit periodic variation whose frequency is similar to that of the internal population periodicity, then population growth is periodically amplified. Thus, Nisbet and Gurney [48] analyze age-structured species whose intrinsic, damped-oscillatory population growth pattern resonates with some external environmental quantity, which exhibits periodic variation. Nisbet and Gurney show that, in such cases, the effect of the external oscillations is strongly amplified and large population oscillations may arise from small driving oscillations. These authors argue that age-structure effects can cause such resonance when the frequency of the driving oscillations is equal to, or to an integral multiple of, the reciprocal of the duration of the infertile phase.

Agur and colleagues obtained comparable results in several complex life-cycle population models. In these models populations are subjected to a loss process due to randomly occurring environmental disturbances that are effective only during a portion of the life-cycle. The models were studied over a large range of time-scales of the environmental change and for different degrees of variance in the system parameters [1, 2, 12, 16]. Analysis shows that the mean extinction time has a strong non-monotonic dependence on the relation between the duration of the disturbance-resistent life-stage and the period of the environmental disturbance. This effect, *the Resonance Phenomenon*, was found at integer and fractional multiple of this relation. Using non-Markov probabilistic models it is shown that, when the disturbance and the resistant stage have comparable time scales, population persistence can increase with increasing disturbance duration. Persistence in all harshly varying environments is shown to depend on the level of synchronization of the environmental and population processes. These results are independent of the exact details of the deterministic equation, whereas the distribution pattern of intervals between disturbances appears to determine the general pattern of extinction. Moreover, the Resonance Phe-

nomenon may depend on a simple relation of the parameters, as in [2, 7, 8, 9, 12, 25], or it may be a complex implicit relation of the temporal parameters, which can only be approximated heuristically [14, 59].

2.1 A Simple Model for Populations with Complex Life-Cycle that are Subjected to Stochastic Environmental Disturbances

Populations with complex life-cycle, in regimes of harsh environmental disturbances whose time-scale is comparable to that of the population generation time, have complicated dynamics. In contrast, model's simplicity is a prerequisite for its formal analysis. For deciphering the universal laws underlying these dynamics one is required to trade-off the detailed description of population structure for achieving analytic tractability and, hence, for uncovering the dynamic rules underlying the model [2].

Thus, it is assumed in [2] that the environment is characterized by alternating harsh and favorable episodes. Population's complex life-cycle is clustered into two main life-stages, with respect to the environmental disturbance: a juvenile stage of length τ, resistant to the disturbance, and an adult, susceptible, stage, which produces juveniles continuously. Harsh disturbances, of duration, δ, completely obliterate all adults. The duration of the intervals between disturbances, i.e. the favorable episodes, ω, is assumed to be strictly positive (see Fig. 1). The rate of population increase is not described explicitly. Rather, it is just assumed to be large enough to guarantee that as long as there is recruitment in an interval between disturbances some adults will persist to the end of that interval. Other details of the deterministic population dynamics are ignored. This model represents an extreme case of harsh conditions, having no birth during the unfavorable episode.

Recruitment in any given interval between disturbances can be committed by juveniles born during one or more of the preceding intervals, depending on the relative time-scale of the biological and environmental periodicity. Thus, the relative time scale, N, of a given system is defined as the maximal number of environmental disturbances that can occur in one biological generation. It is shown hereafter that this definition plays an essential role in the analysis of

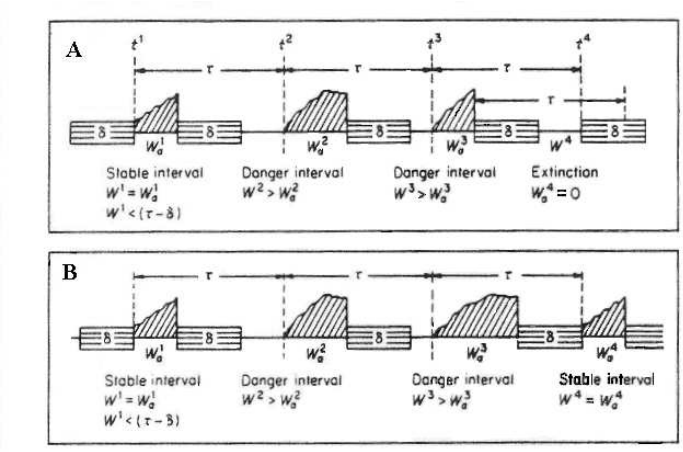

Figure 1: The dynamics of the system in the region $1 < \tau/\delta \leq 2$. **A.** The process leading to extinction. The stable interval of duration, $W^1 < (\tau - \delta)$, initiates a sequence of danger intervals. Extinction occurs in the nth interval, $W_a^n = 0$, when $W_a^{n-1} + W^n \leq (\tau - \delta)$. **B.** The system returns to a "stable state" in the nth interval, $W^n = W_a^n$, when $W_a^{n-1} \geq (\tau - \delta)$.

extinction patterns.

Notations: Parameters and variables to be used in this section are defined as follows:

τ — duration of the juvenile stage

δ — duration of environmental disturbance

φ — disturbances frequency (so that φ^{-1} denotes the period of disturbance)

W^i — duration of the interval i between two subsequent disturbances

W_a^i — episode of adult presence during the i-th inter-disturbance interval

t^i — epoch of initiation of adult recruitment in interval i

2.1.1 Disturbances and resistant form having comparable time scales

This section is intended to describe the pattern of extinction when disturbance period and the population generation time are of comparable durations, ($N = 1$), and to prove that in such systems the time to extinction increases with increasing duration of disturbance.

In the region

$$1 < \tau/\delta \leq 2 \tag{1}$$

$N = 1$, for all distributions of intervals. When τ and δ obey (1) and as long as the intervals are large enough, the epoch of initiation of adult recruitment in an interval, i, t^i, coincides with the initiation of that interval. Once there occurs an interval whose duration, W^i, obeys

$$W^i < (\tau - \delta)$$

then the initiation of recruitment in all subsequent intervals will have a fixed period, τ, with the position of the epoch $t^{i+1}, t^{i+2}, ...$, varying within inter-disturbance intervals (Fig 1). Population is extinct

upon the occurrence of an interval, the nth, say, which is too short to include the epoch t^n, so that recruitment is fully overlapped by the following disturbance. The state of the population in any interval belongs, therefore, to one of three categories:

1. *A stable state*, when the epoch t^i coincides with the initiation of the interval, i, so that the period of adults, W_a^i that commences with t^i and terminates with the beginning of the next disturbance obeys

$$W_a^i = W^i.$$

2. *A danger state*, when the epoch t^i falls within the interval i, so that

$$W_a^i < W^i.$$

3. *Extinction*, when the epoch t^i coincides with a disturbance, so that

$$W_a^i = 0.$$

The inter- relationships between these three states is sketched in Fig. 2.

The process of extinction is described, then, by the episodes of adult presence in the chain of intervals. Let W^i be an interval in a stable state so that

$$\begin{aligned} W^1 &= W_a^1 \\ W^1 &< (\tau - \delta). \end{aligned} \tag{2}$$

From condition (1) it is clear that the following interval is in a danger state, $W_a^2 < W^2$ (see Fig. 1A). W^2 and all subsequent intervals are danger intervals as long as each one of them contains an episode of adults satisfying

$$(\tau - \delta) \geq W_a^i > 0$$

$$W_a^n = 0 \quad \text{if } W^n \leq (\tau - \delta) - W_a^{n-1} \tag{3}$$

$$W_a^{n-1} = W^{n-1} - (\tau - \delta) + W_a^{n-2} \tag{4}$$

and from this recursion and the first equation in (2) we obtain

$$W_a^{n-1} = \sum_{i=1}^{n-1} W^i - (n-2)(\tau - \delta). \tag{5}$$

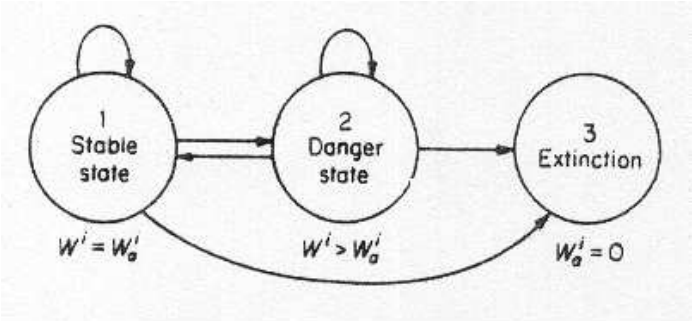

Figure 2: The state-chart of population dynamics, determined by the episodes of adults within favorable periods. The trajectory leading from a stable state to extinction, directly or through the intermediate, danger state, is described by equation (6). The trajectory from a stable state to a danger state and back to a stable state is described by equation (7).

Thus, the conditions for extinction in the nth interval are

$$\begin{aligned} W^1 &= W_a^1 \\ W^1 &< (\tau - \delta) \\ \sum_{i=1}^{n} W^i &\leq (n-1)(\tau - \delta). \end{aligned} \tag{6}$$

If $W_a^n \geq (\tau - \delta)$, then the next interval will be stable (Fig. 1B), that is:

$$\text{if} \quad W_a^n \geq (\tau - \delta), \quad \text{then} \quad W_a^{n+1} = W^{n+1}.$$

Now,

$$W_a^n \geq (\tau - \delta) \quad \text{if} \quad W^n \geq 2(\tau - \delta) - W_a^{n-1},$$

and from (5) it is clear that the conditions for returning to a stable state in the interval $n+1$ are

$$\begin{aligned} W^1 &= W_a^1 \\ W^1 &< (\tau - \delta) \\ \sum_{i=1}^{n} W^i &\geq n(\tau - \delta). \end{aligned} \tag{7}$$

The population will still be in a danger state in the nth interval if:

$$n(\tau - \delta) > \sum_{i=1}^{n} W^i > (n-1)(\tau - \delta). \tag{8}$$

From the system (7) and the second condition in (6) it is evident that for a given distribution of intervals extinction occurs earlier, both in calendar time and in the count of intervals (the *period index*), the larger is the value of $\tau - \delta$. The process returns to a stable state earlier for smaller values of $\tau - \delta$. This conclusion can be restated in the following manner.

Corollary 1. For any distribution of the process $(W^1, W^2, W^3, ...)$, the extinction time and the extinction period index in environment B are stochastically larger than those in environment A, when

$$\tau/2 \leq \delta_A < \delta_B < \tau.$$

Corollary 2. For any distribution of the process $(W^1, W^2, W^3, ...)$, the extinction period index of population B are stochastically larger than those of population A, when

$$\tau_A/2 \leq \delta < \tau_B < \tau_A.$$

Maximum synchronization of population growth with the inter-disturbance interval under the described stochastic environmental process is achieved when

$$\tau/\delta \to 1^+.$$

2.1.2 Disturbances of a relatively small time scale

The dependence of the average time to extinction on the frequency of disturbance will be analyzed for $N = 2$. Extinction occurs here in the interval n, given that

$$W_a^{n-2} > 0$$

if

$$W_a^{n-1} = 0 \quad \text{and} \quad W_a^n = 0. \tag{9}$$

The probability of the event, described in equation (9), depends on the state of the interval $n-3$. Given $W_a^{n-3} > 0$, the conditions for equation (9) are defined as follows:

$$W_a^{n-3} + W^{n-2} + W^{n-1} \leq \tau - 2\delta \tag{10}$$

and

$$W_a^{n-2} + W^{n-1} + W^n \leq \tau - 2\delta \qquad \text{(Fig. 3A)} \tag{11}$$

or

$$W_a^{n-2} \geq \tau - 2\delta \tag{12}$$

and

$$W_a^{n-1} \geq \tau - 2\delta \tag{13}$$

and

$$W_a^{n-2} + W^{n-1} \leq \tau - \delta \qquad \text{(Fig. 3B)} \tag{14}$$

or

$$W_a^{n-2} + W^{n-1} + W^n \leq \tau - 2\delta$$

and

$$W^{n-2} \geq \tau - 2\delta \qquad \text{(Fig. 3C)} \tag{15}$$

The conditions for extinction during W_a^{n-3}, are easy to define. Doing so, it becomes evident that extinction probability is always higher when $W_a^{n-3} > 0$. Moreover, when the frequency of disturbance is very large, extinction will most probably occur through the combination of events (10) and (11). Note that (10) and (11) can be generalized for all relative time scales: for all N and large frequency of disturbance, the condition for $W_a^n = 0$ is given by

$$W_a^{n-N} + \sum_{i=n-N+1}^{n} W^i \leq \tau - N\delta. \tag{16}$$