Use of real time leukaemia data to validate model predictions based on analyses and computer simulations

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Received 5 January 2001; revision accepted 18 April 2001

Abstract. Predictions arising out of a mathematical model that describes the expansion of leukaemia from a diffusion-orientated perspective are critiqued and validated by employing available real time data. Based on agreements found between model predictions and the data, but mindful of the limitations it presents, it is concluded that the model could be used to describe the dynamics of normal and abnormal cells in leukaemia. It is suggested that further studies of the behaviour of certain normal cell types in contrast to abnormal cells during leukaemic development could engender additional insights into leukaemia and its treatment.

INTRODUCTION

In a recent article (Afenya & Bentil 1998), we proposed a mathematical model to describe the development of leukaemia from a diffusion-orientated viewpoint. We used the model to study the space-occupying effects of the leukaemic clone during leukaemic expansion by performing model analyses and simulations and arriving at certain insightful predictions about human leukaemia. However, at that time, an important ingredient that was missing from our investigations was a plausible link between the model predictions and real time definitive data that was difficult to find from the literature. Recently, data obtained from Dr Wilson Hartz, Jr. (until recently the Attending Internist and Hematologist at Sherman Hospital in Elgin, Illinois) and Dr Yoshihito Yawata of Kawasaki Medical School in Japan has enabled us to conduct investigations into developing a realistically tenable basis for our model predictions. Consequently, in this article we use the data to critique and assess the validity of the analytical and simulation-based predictions generated by the model. In the process, we will also use the data to affirm or refute certain conjectures that we made in Afenya & Bentil (1998).

It is worth mentioning that remarkable advances have been made in the fight against cancer. Advances in cytogenetics and molecular biology, for example, are elucidating the aetiology of the leukaemias. Treatment outcomes for certain cancers with or without haematopoietic growth-factor support are also providing the optimism of cure for some malignant diseases. Despite the advances, however, biomedical science still faces challenges in dealing with the cancers. A number of issues that need to be addressed include treatment optimization and quantification of disease (Devita 1997; Morley 1998) and it is our conviction that consideration of such issues

engenders interdisciplinary approaches that give mathematical modelling an important role to play in the fight against cancer. It is within this framework that this article gains significance. In this light, we believe that mathematical models could play their part if they could reflect and describe some of the characteristics and dynamics of observed biomedical phenomena thus giving clinicians an option of avoiding experiments that may turn out to be risky and ethically challenging. It is precisely in this spirit that we make this presentation in this article.

REVISITING THE MODEL

In presenting the model described by Afenya & Bentil (1998), we note that leukaemia is characterized by a situation in which the malignant clone expands at the expense of normal myeloid or lymphoid lines and suppresses or impairs normal myeloid or lymphoid cell growth (Schrier 1995). Leukaemia cells also act to inhibit the colony-forming capabilities of normal proliferative cells and disrupt the smooth functioning of the entire haematopoietic system. Following the work of Afenya & Bentil (1998), it could be assumed that normal and leukaemic cells exist side by side as single cell populations that obey apoptotic mechanisms, Gompertzian growth kinetics, and diffusive processes, respectively. However, the leukaemic clone exhibits a negative and inhibiting effect on the normal population through interactive and other mechanisms. As a consequence, the spatio-temporal model for the spread of the normal and leukaemic cells could be stated in words as follows:

(Rate of change of the leukaemic cell population) = (Gompertzian growth of leukaemic cells) – (leukaemic cell loss) + (leukaemic cell diffusion);

(Rate of change of the normal cell population) = (Gompertzian growth of normal cells) – (normal cell loss) – (normal cell interaction with leukaemic cells) + (normal cell diffusion).

The mathematical formulation of the model can be found in the Appendix. Since the full details of the mathematical analyses and computer simulations of the model can be found in the work of Afenya & Bentil (1998), we will pass on to considering the predictions of the model and how they match or compare with patient data in the next section.

RESULTS FROM VALIDATION OF THE MODEL WITH REAL TIME DATA

In this section we enumerate and discuss the predictions arising from the model and confirm or invalidate them by using the available data. A summary of the specific predictions (Afenya & Bentil 1998) are restated as follows:

- 1 The model predicts the existence of two realistic steady-state sets; one in which there is a coexistence of normal and leukaemic cells and the other in which there are leukaemic cells and no normal cells.
- 2 The steady state that represents a situation of coexistence between normal and leukaemic cells breaks down in the face of small space–time perturbations while the steady state with only leukaemic cells and no normal cells persists. The persistence of this particular steady state indicates that there is an ultimate situation in which normal cells are replaced by leukaemic ones.

- 3 The breakdown in the steady state of coexistence may occur when there is a large leukaemic diffusive coefficient compared to a small normal diffusive coefficient. It may also occur when the size of the space of distribution is relatively large. This may mean that in the leukaemic state normal cell survival cannot occur unless this state is itself disrupted by an external agent, in this case a drug.
- 4 There may be accumulations of cells at certain sites and depletions at other sites and through such processes leukaemic cells may occupy sites of normal cells as the propagation of spatial heterogeneities occur. As a result, it may be suggested that the positions occupied by the leukaemic cells as they expand, may be very fertile areas that are rich in nutrients needed for haematopoiesis. This is because those positions used to be occupied by the displaced normal cells. Thus, leukaemic cell numbers may increase very rapidly.
- 5 The rapid increase in leukaemic cell numbers may also be tied to the phenomenon of contact inhibition through which normal cell production is disrupted and leukaemic cell growth is stimulated possibly over a wide region of space.
- 6 Upon introduction of leukaemic cells, existing normal cell colonies go through a process of shrinkage as their positions are invaded by emerging colonies of abnormal cells. The resulting leukaemic dominance may cause damage to and disturb the colony-forming capabilities of the normal cells.

It is important to mention that these predictions stemmed from measuring, from an analytical and numerical viewpoint, the relative sizes of the normal and abnormal populations at the equilibrium and at the spatio-temporal periods of the evolution of the model; the relative sizes of the respective diffusive coefficients of the normal and abnormal cells; and the size of the space of distribution.

In relation to Predictions 1, 2, and 3, the persistence of the steady state in which there are no normal cells portrays a situation in which abnormal cells replace normal cells and dominate the blood and marrow. This is confirmed by what can be observed in Fig. 1a where a biopsy shows that leukaemic blast cells in acute myeloblastic leukaemia (AML) replace normal bone marrow cells and end up occupying the entire marrow.

Predictions 4 and 5 mean that spatial heterogeneities may persist when leukaemia cells are introduced causing these cells to aggregate and form clusters very rapidly via diffusive mechanisms. The abnormal cells occupy spaces possibly designated for normal cell growth. Figure 1b,c, which represent AML without and with maturation, respectively, confirm this prediction. The clustering of the cells can be observed in these figures.

In Fig. 2b, the model simulations predicted that the abnormal cells initially stay at a reasonably low level for some period of time within the space of distribution and later rise abruptly at some point in time and one-dimensional space possibly due to a weakening of the body's control mechanisms. While this is happening, the normal cells decrease in population towards very low levels as is shown in Fig. 2a. To verify this we considered patient data obtained from Dr Wilson Hartz, Jr. The profiles shown in Fig. 3a,b and Fig. 4 are on a patient (Patient A) who initially presented with diabetes mellitus and started receiving the doctor's attention on April 21 1992 (Day 0). This patient was later diagnosed with acute myelomonocytic leukaemia and was admitted for intensive chemotherapy around January 25 1996. The profiles in Fig. 3a,b and Fig. 4 cover the portion of the data indicating cell behaviour before active treatment. Figure 3b is a three-dimensional enhancement of Fig. 3a. This enhancement has been provided to facilitate a better visualization of the two-dimensional rendering shown in Fig. 3a. It is important to observe that the data shown in Fig. 3b are uniform in the direction of the 'false' third dimension and thus retain all their attributes from Fig. 3a. We took the abnormal cells to be represented by abnormal

Figure 1. Biopsy specimens in AML. (a) A biopsy specimen stained by haematoxylin-eosin in which normal components of the bone marrow are totally replaced by leukaemic blast cells in AML. (b, c) Clustering or aggregation of abnormal cells possibly at sites originally occupied by normal cells due to the persistence of spatial heterogeneities engendered through diffusive mechanisms. The clustering phenomenon shown in (b) relates to AML without maturation and that in (c) depicts AML with maturation.

blasts with their behaviour shown in Fig. 3a,b and the normal cells were represented by segmented neutrophils (SEGS) in Fig. 4; a justification for this is discussed in the next section. It can be observed from the profile in Fig. 3 that the blast counts remained at zero level (the normal level), rose slightly and fell back to zero level between Days 984 and 993, and went back to the

Figure 1. *Continued*

normal level after Day 993. Even though the count rose again slightly around Day 1001 and between Days 1091 and 1122 it could be argued that a semblance of normal behaviour in blast count existed until after Day 1190. The blast count effectively ceased to be normal after this day and confirms the model prediction depicted in Fig. 2b. In considering the prediction shown in Fig. 2a about the normal cells, we observe from measurements in Fig. 4 an irregularly oscillatory pattern of decrease in segmented neutrophil numbers (which have a normal range of 31–66% described by the upper and lower thick horizontal lines in the figure) towards a low level. It is important to note that the SEGS decreased towards the lower bound of their normal range around Day 988, and went below this lower bound between Days 1091 and 1122, and beyond Day 1190 till the end of the profile. These days are in correspondence with the times (or time ranges) when the blasts displayed abnormal behaviour in Fig. 3. Thus, even though these neutrophils oscillate irregularly within their normal range for some period of time, they essentially display a decreasing trend by going below the lower bound of their normal range for a relatively substantial period of time that spans up to the end of the profile. This decreasing trend becomes particularly pronounced towards the end of the profile. This decreasing pattern is captured by the decaying curve that is fitted to the profile in Fig. 5. Therefore, the prediction associated with normal cell behaviour shown in Fig. 2a is valid, to a reasonably approximate extent, if compared to observations in Figs 4 and 5. We must mention that Figs 4 and 5 are the same. The only difference is that Fig. 5 is obtained by fitting the decaying curve to the data in Fig. 4 resulting in an adjusted horizontal axis in Fig. 5 to accommodate the curve and the data profile.

To further investigate the validity of the predictions expressed in Fig. 2a,b, we considered data on a second patient (Patient B) of Dr Wilson Hartz, Jr. who was diagnosed with chronic granulocytic leukaemia (CGL). The patient started receiving the doctor's attention on March 21 1981 (day 0) and started receiving chemotherapy on March 21 1994. In considering data on this patient we again took the blast counts shown in Fig. 6a,b to represent abnormal cells and the segmented neutrophil counts shown in Fig. 7 represented the normal cells (see the next section

Figure 2. Evolution of normal and leukaemia cells in time and one-dimensional space. The normal cell population goes through a process of decay and moves away from its homeostatically steady level in (a), upon introduction of a rapidly proliferating abnormal cell population that assumes dominance, as shown in (b). The normal (N) and leukaemic (L) populations represented on the vertical axes in (a) and (b), respectively, are multiplied by 10^{10} .

Figure 3. Behaviour of the blasts of Patient A. (a) Even though the blasts rise slightly above their normal zero level at certain instances of time, a semblance of normality is maintained for a reasonable period of time before such normality ceases completely. (b) Three-dimensional enhancement of the blast behaviour in (a). This is shown for better visualization of the data. The data is uniform in the direction of the 'false' third dimension and it retains all its attributes from the two-dimensional rendering in (a).

Figure 4. Behaviour of the segmented neutrophils of Patient A. The cells oscillate irregularly within their normal range represented by the upper and lower thick horizontal lines but do so in a decreasing fashion. They decrease considerably below their normal lower bound towards the end of the profile when blast crisis occurs.

Figure 5. The decaying pattern in the irregular oscillations of segmented neutrophils of Patient A is captured by a decreasing curve that is fitted to the data in Fig. 4.

Figure 6. Blast behaviour in Patient B. (a) The blast counts effectively cease being normal after Day 3982 even though some abnormal behaviour occurs before this day. (b) Three-dimensional enhancement of the blast behaviour in (a). This is shown for better visualization of the data. The data is uniform in the direction of the 'false' third dimension and it retains all its attributes from the two-dimensional rendering in (a).

Figure 7. Segmented neutrophil behaviour of Patient B. (a) The cells oscillate irregularly with large and small amplitudes at various times within their normal range represented by the upper and lower thick horizontal lines. They also decrease below and go above their normal range at various times before taking a dive towards the end of the profile. (b) The decaying curve fitted to the data in (a) reflects and shows the net resultant effect of the irregularly oscillatory behaviour exhibited by the segmented neutrophils of this patient.

for a justification). Once again the profiles showed in these figures cover portions of the data that indicate cell behaviour before treatment and Fig. 6b is a three-dimensional enhancement of Fig. 6a. This enhancement has been provided to facilitate a better visualization of the two-dimensional exposé of Fig. 6a. We note that the data shown in Fig. 6b is uniform in the direction of the 'false' third dimension and thus retains all its attributes from Fig. 6a. Following similar arguments raised earlier, it can be noticed from Fig. 6 that the blast counts effectively ceased being normal after Day 3982 even though some abnormal behaviour occurred before this day. This further confirms the prediction depicted in Fig. 2b about the behaviour of leukaemia cells during leukaemic development. In Fig. 7a a semblance of normality is maintained in segmented neutrophil numbers with irregular oscillations taking place within the normal range of 31–66% described by the upper and lower thick horizontal lines in the figure. However, it is notable that around Days 0–42, 847–1238, 3961–3963, and beyond Day 3982, the segmented neutrophil counts either went below or decreased towards their lower bound and these days correspond to the time periods when the blast counts behaved abnormally. It is apparent from Fig. 7a that neutrophil numbers remain seemingly normal and irregularly oscillatory for a relatively longer time frame but experience occasional decreases that become pronounced towards the end of the profile. By observing the profile displayed in Fig. 7a, it could be argued that the oscillations in neutrophil numbers occur within their normal range making it difficult to make a claim about a decreasing trend in this case. However, a closer look at the profile, based upon our measurements, indicates that the oscillations take place with irregular amplitudes, some being large and a number of them being small. Therefore, the decaying curve that is fitted to the data in Fig. 7b captures the net effect of the oscillations that go below and above their normal range coupled with the irregularly large and small amplitudes occurring at various points in time. It basically reflects a resultant effect of decline if the irregular oscillations were 'smoothened out.' Thus, without ignoring the irregular oscillations in neutrophil numbers depicted in Fig. 7a that are not directly accounted for in Fig. 2a, it may be appropriate to say that this resultant effect of decline particularly towards the end of the graphs in Figs 7a and b in part gives validity to the essence of the prediction displayed in Fig. 2a about the behaviour of normal cells during leukaemic expansion. We must point out that Figs 7a and b are the same. The only difference is that Fig. 7b is obtained by fitting the decaying curve to the data in Fig. 7a resulting in an adjusted horizontal axis in Fig. 7b to accommodate the curve and the data profile.

DISCUSSION AND CONCLUDING REMARKS

It was clearly evident from the data under study that the blasts depicted in Figs 3 and 6 could be unambiguously taken to represent abnormal cells. The same situation did not exist in choosing SEGS to represent normal cells because the data provided information on various other normal cell types – platelets, white blood cells (WBCs), nucleated red blood cells (NRBCs), promyelocytes, myelocytes, metamyelocytes (MM), eosinophils, basophils, and band neutrophils (BN) – to name a few. Since we are dealing with leukaemia, we opted to focus our attention on the matured neutrophils (MM, BN, and SEGS) that supposedly perform various functions of protecting the human body against pathological situations (Hoffbrand & Petit 1984). Here, it is appropriate to mention the widely held view that BN and mostly SEGS get released into the circulation where they constitute the blood pool of functional polymorphonuclear neutrophils (Afenya 1996). Therefore, they play the important roles of inhabiting the marrow and the blood that are areas within the space of distribution that leukaemia cells also populate.

Table 1. Correlation and *P*-values on Patient A

	Correlation	<i>P</i> -value
Blasts versus SEGS	−0.4404	0.0000611
Blasts versus BN	−0.0661	0.568
Blasts versus MM	−0.1123	0.3306

Table 2. Correlation and *P*-values on Patient B

	Correlation	<i>P</i> -value
Blasts versus SEGS	−0.3041	0.0042
Blasts versus BN	0.2249	0.036
Blasts versus MM	−0.2621	0.0142

In developing a scheme for arriving at the choice of SEGS to represent normal cells, we took note of the observation that the presence of abnormal cells in leukaemia leads to a depletion of normal cells (Schrier 1995; Afenya 1996; Afenya & Bentil 1998). This suggests the existence of a kind of 'inverse' relationship between leukaemia and normal cells that ultimately benefits the cancerous cells. This inverse relationship can also be discerned from noted decreases, as we discussed in the previous section, in segmented neutrophil numbers below their lower bound at the same instances of time when the blasts rise above their normal level. Capturing the essence of this relationship produced the choice of SEGS. In arriving at this choice to at least a first approximation, we computed and compared the correlation between blasts and SEGS, blasts and BN, and blasts and MM, respectively, for Patients A and B. Then we picked the one with the most negative value along with the most suitable *P*-value, on each patient (the results are shown in Tables 1 and 2).

The correlation values shown in Tables 1 and 2 for blasts versus SEGS do suggest a pattern of decrease in segmented neutrophil numbers in the two patients as the blast counts increase. This assertion goes to further support the noted decreases in segmented neutrophil numbers observed in Figs 4, 5, 7a, and 7b despite the irregularly oscillatory behaviours discussed in the section above. Following this, it may be plausible for us to suggest that further studies of the behaviour exhibited by SEGS and possibly other normal cell types in contrast to blasts during leukaemic development could give valuable insights into how to approach treatment of the disease and we plan to pursue this from a mathematical modelling viewpoint. A look at the data on Patients A and B shows that leukaemia cells, in the acute or chronic case, obey the dynamics illustrated in Fig. 2b. The only difference that we observe in their behaviours stems from a longer time to reach blast crisis in the chronic case than in the acute case as can be seen in Figs 3 and 6. Upon this basis, our conjecture in Afenya & Bentil (1998) about an oscillatory evolution of abnormal cells towards blast crisis in the chronic leukaemias may not be correct. On another note, a direct comparison of normal cell dynamics exhibited in Fig. 2a to the patient data in Figs 4 and 7a shows that the model captures the full behavioural profile of the declining trend of normal neutrophils of Patient A. Even though the evidence from the fitted curve in Fig. 7b and Table 2 support a pattern of decline in neutrophil numbers of Patient B that reflects the essence of Fig. 2a, we deem it necessary, pending further investigations of similar patient data, to remark that the model only partially captures the complete dynamic of this patient's normal neutrophil profile that appears chaotic or irregularly oscillatory (from measurements) over a reasonable

portion of time. Thus, the chaotic dynamics exhibited by the SEGS in Figs 7a and b over a significant time frame presents a reasonable degree of doubt in confirming the correctness of the part of the conjecture in Afenya & Bentil (1998) about an oscillatory evolution of normal cells towards blast crisis in the chronic leukaemias. Therefore, cognisant of the limitations related to work with data on only two patients, a kind that in any case is scarce and not readily available, we may conclude that the model could be used to describe the full dynamics of normal and abnormal cells in acute leukaemia (AL) and the dynamics of abnormal cells in chronic leukaemia (CL). It may have to be modified to account for the observed irregular oscillations in neutrophil numbers if it should be used to describe the dynamics of such cells in CL at small to intermediate time instances. Most importantly, however, noting that there is a longer time course towards blast crisis in CL as can be seen from the behaviour in Figs 7a and b in comparison to Figs 4 and 5, the model could be used to capture the dynamics of the normal neutrophils in CL at large time instances. It is of interest to remark that there is relative ease in visualizing the data on Patients A and B from a three-dimensional perspective as displayed in Figs 3b and 6b than in the plane described by Figs 3a and 6a. This may lend further credence to space–time diffusion-orientated approaches to modelling cancer and its treatment since they tend to present the requisite context for three-dimensional reasoning.

At this juncture, it may be safe to say that the agreements found between our model predictions and the data seek to confirm the validity of assumptions we have made in a number of situations (Afenya 1996, 1998; Afenya & Calderón 1996, 1999, 2000; Afenya & Bentil 1995, 1998), to guide the modelling process and arrive at the ensuing conclusions arising therefrom, in our investigations of leukaemia. It is particularly notable from the data that during the times or time intervals when a semblance of normality is maintained in the blast counts, the SEGS stay in their normal range even though they oscillate irregularly in a decreasing fashion in this range. When the blasts rise above their normal zero level, the SEGS either decrease below their normal lower bound or show a tendency of decreasing below this bound. This behaviour may suggest situations in which abnormal cells are replacing or suppressing the normal ones within the space of distribution and give further support to the model predictions in this regard. We hope to keep focusing our attention on investigating more data sets with the view to proposing space–time models that could give insight into the disease states and their treatment. Without diminishing the importance of models that are solely time-dependent, we believe that space–time models may be effective in addressing and capturing the characteristics of heterogeneity that is universally expressed by cancer cells (Rose 1998). It is important to remark that patient data of the kind used in this article is hard to find because diseases such as leukaemia normally get detected at late stages in people who report symptoms and have to be treated immediately to avoid fatalities (Rohatiner & Lister 1996). Nonetheless, we will be interested in working with investigators who have case histories of patients they have been working with and can make such patient data available. This will enable us to continue seeking modifications to our models with the aim of creating model profiles that mimic real time data and give insight into treatment of different disease states that ultimately contribute to an expansion of the various treatment options available to clinicians.

ACKNOWLEDGEMENTS

The data shown in Fig. 1a,b,c were used with the permission of Dr Yoshihito Yawata of Kawasaki Medical School and TOA Medical Electronics in Japan and the data depicted in Figs 3–7 is due

to the courtesy of Dr Wilson Hartz, Jr. who until recently was the Attending Internist and Hematologist at Sherman Hospital in Elgin, Illinois, USA. The author will like to express his sincere gratitude to these two medical doctors for granting him access to their data. He thanks Drs Suneel Mundle and Azra Raza of the Rush Cancer Institute of Rush Medical University in Chicago for the fruitful discussions they engaged in with him during the preparation of this article. He is also thankful to the anonymous referees whose comments and suggestions aided in the revision of this article. Figure 2 was reprinted from Afenya & Bentil (1998) with permission from Elsevier Science. The author was partially supported by National Science Foundation (NSF) grant number DMS-9973944 and a research grant and sabbatical from Elmhurst College.

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APPENDIX

The mathematical representation of the model (Afenya & Bentil 1998) is as follows:

$$L_t = gL \left(\log_e \frac{A}{L} \right) - fL + d_l \nabla^2 L, \quad g > 0, f > 0 \quad (1)$$

$$N_t = aN \left(\log_e \frac{A_n}{N} \right) - bN - cNL + d_n \nabla^2 N, \quad a > 0, b > 0, c > 0 \quad (2)$$

with initial conditions

$$N(\mathbf{s}, 0) = N_0, \quad L(\mathbf{s}, 0) = L_0, \quad (3)$$

where the parameters A and A_n are the asymptotic bounds on the leukaemic and normal cell populations, respectively. The quantity L represents leukaemia cells and N represents normal cells. Since leukaemic activity is taking place in the body, which can be described as a closed environment (Murray 1999), it is appropriate to impose zero flux boundary conditions of the form:

$$(\mathbf{n} \cdot \nabla) \mathbf{W} = 0 \quad (4)$$

where $\mathbf{W} = (L, N)$ and $\mathbf{n}$ is the unit outward normal. The parameter a is the intrinsic growth rate or growth speed of the normal cells and b is their death rate. Parameter c is a measure of the degree of inhibition of the normal cells with respect to the leukaemic cells. The parameter g is the intrinsic growth rate or growth speed of the leukaemia cells and f is their death rate. The diffusive coefficients for the leukaemic and normal cell populations are given by d_l and d_n , respectively.