

A mathematical model of absorbing Markov chains to understand the routes of metastasis

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Abstract—Metastasis is a complex and multi-step stochastic process. The study of the probabilities of generating a tumor from a primary site in another organs is the aim of this work. Based on statistics of National Institute of Cancer of Argentina (INC), a characterization of the routes of metastasis for the principal organs is presented by using Absorbing Markov chains. The metastasis propagation from different primary sites towards secondary and tertiary sites is also shown, emphasizing the relation and analysis about absorbing states.

Keywords-Metastasis; Complex Systems; Mathematical Modelling; Absorbing Markov chains

I. INTRODUCTION

Cells have a specific and stipulated time of death (apoptosis) and reproduction rate to maintain cell balance. A tumor is the result of an uncontrolled growth of abnormal cells or when cells lose the ability to die. These cells form accumulations that affect the normal functioning of the organs, and can spread to other organs so as to cause metastasis. Metastasis is the spread of circulating tumor cells (CTC) from a primary site to near or distant locations by different ways. This depends on the organ and its initial localization through either the bloodstream or the lymphatic

system (a collection of vessels that carry fluid and immune cells)[1], [2].

Markov chains are used to model different natural systems based on statistics and applications ([3], [4]), making the dynamic and continuous processes where the states depend only on the actual state and not as a result of previous events[5]. Recently, some works ([6], [7]) give different approaches by using Markov chains in metastasis processes from the lung, where mechanisms of progression and time scales of systemic disease are quantized. In the present work, we use absorbing Markov chains to analyse the metastasis transmission of solid tumors of different organs: from the primary site to a secondary site (called metastasis from primary site), and from there to a tertiary site (metastasis of secondary site) for the principal cancers in Argentina. The probabilities of having a tumor in a tertiary or secondary site from a primary site and their differences depending on each organ is analysed, as well as the probabilities that from a primary site ends in those organs that have very low probability of spreading CTCs are calculated. Finally, the steps (meaning the stages between metastasis from a primary to secondary or tertiary

site) based in absorbing states (in our case, organs with low probability of generating metastasis) are found. The aim of the present work is to understand how the organs are related to each other giving a characterization of the routes of metastasis.

The metastasis are different for males and females. However the analysis performed here is similar in both cases, although different organs are affected (ovaries, vagina or uterus in females and prostate or testicles in males). In this paper we refer only the metastasis in males as a case study.

This work is organized as follow: In Section II a brief description of the methodology is given; Section III is devoted to describe transition matrices and absorbing states; The transition matrix for tertiary sites is shown in Section IV; An analysis of expected number of steps and probability of absorption by absorbing states is found in Section V; Finally, comments and conclusions are drawn in Section VI.

II. METHODOLOGY

The Markov chain transition matrix P was assembled and it is determined by the number of organs with higher probabilities of developing metastasis. This matrix shows the probability that an organ can be reached by CTCs[8] from another organ and has been built under the assumption of developing metastasis. Up to now, three leading routes of metastasis are known: **Hematogenous (blood circulation), lymphatic and transcoelomic**. With this information, the statistics of National Institute of Cancer of Argentina[9] of the principal tumors and quantitative data on the main organs affected depending on the primary site (obtained from National Cancer Institute at the National Institutes of Health of United States)[10], we performed the graph (depicted in Fig. 1) showing the most common tumors and the principal sites where they can generate metastasis.

The graph was designed by free software *Visone 2.15*[11]. The size of the nodes represents

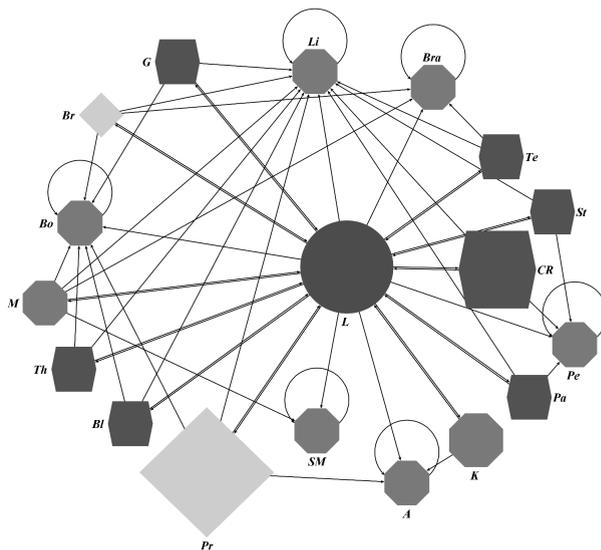


Fig. 1: Graph for the principal links of metastasis for tumors in males based in statistics. The name of the organs were referred by a symbol as depicted in Table I.

the proportion of cases for the main tumors mentioned in reference [9]. The connection of these nodes (the links) is based on the main sites of metastasis, for each specific organ, according to the data of the reference [10]. Besides, the shapes of the nodes depends on the amount of linked organs: Circle, 6 or more organs to propagate metastasis; Rhombuses, 4 or more; Hexagons, 2 or more; and finally Octagons, organs with low probability of propagate metastasis. It is important to note that the organs with low probability of generating metastasis, compared to the rest, are shown in the graph as a link on themselves (not to be confused as to metastasize about themselves).

In Fig. 1, it can be seen that the Lung is the principal link. Although the principal primary sites are Prostate, Colon or Rectum, Lung tumor is the most common but usually comes from some primary site, being the principal secondary site ([12], [13]).

TABLE I: Symbols for organs

ORGAN	NAME
Adrenal Gland	A
Bladder	Bl
Bone	Bo
Brain	Bra
Breast	Bre
Colon/Rectum	CR
Gallbladder	G
Kidney	K
Liver	Li
Lung	L
Melanoma	M
Pancreas	Pa
Peritoneum	Pe
Prostate	Pr
Skin/Muscle	SM
Stomach	St
Testicular	Te
Thyroid	Th

III. TRANSITION MATRIX, PROBABILITIES AND ABSORBING STATES

A. Transition matrix and its probabilities

The characterization of metastatic evolution is developed by using Markov chains, based on a network construction from a primary site.

Let X_0 (primary site) be the organ where the tumor was originated, and X_1 the state of the process where the new tumor is formed coming from the primary site and develop metastasis (Note: The transition time, sub index of X , does not refer to a calendar time, it refers to a general time in which has already been observed a new tumor). The probability that an organ develops metastasis from another one is:

$$p_{ij} = P[X_1 = j | X_0 = i] \quad (1)$$

where $i, j = 1, 2, 3, \dots, m$ number of organs.

The values p_{ij} are called *transition probabilities*[14] and have two properties:

- $\sum_{j=1}^m p_{ij} = p_{i1} + p_{i2} + \dots + p_{im} = 1$, since the system must be in one of these states m , the sum of probabilities must be equal to 1.

This means that the elements in any row of the matrix transition must add 1.

- Each element $p_{ij} \geq 0$

Based in the transition probabilities, the *transition matrix* P is given by:

$$P = [p_{ij}], \quad P \in \mathbb{R}^{m \times m} \quad (2)$$

The routes for metastasis from one organ to another are known; although, in the literature, no information is available about their relative likelihood on which organs have an advantage over others. Given this slight uncertainty, the qualitative information ([10], [15]), we assume an equal probability that an organ X_0 (primary site), reaches other one X_1 (secondary site), this is under the assumption a metastasis is detected and based in the possibles routes as previously discussed. For other cases, where there are not predominant organs for metastasis from a specific primary site (according references [10], [12] and [13]), we will assume zero probability in order to work only the predominant sites of metastasis.

Looking at matrix P , if a tumor of a primary site, for example Prostate (Fig. 3a), has a non null probability of developing a new tumor in a secondary site, this will be $1/4$ for L , Li , Bo and Pe . The same considering a tumor in Stomach (3b), that probability will be $1/3$ for Li , Pe and L .

The matrix P is given in the Appendix A. Another way to visualize the matrix P is displayed in the Fig. 2, where, in RGB scale, the probabilities expressed in Eq. 2 can be seen.

B. Absorbing states

It is worth to notice the existence of absorbing states in the system, these are states where it is impossible to leave and are found if any row of the matrix satisfies[14]:

$$p_{ii} = 1 \text{ and } p_{ij} \neq 0 \text{ (if } i \neq j) \quad (3)$$

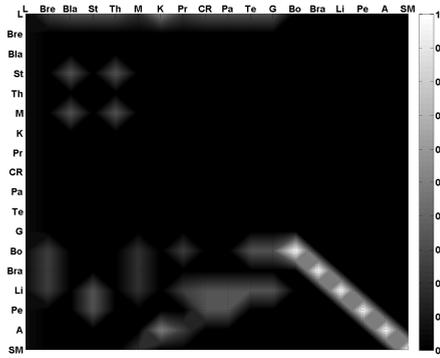


Fig. 2: Visualization of the transition matrix, in gray scale, for secondary sites.

The properties of an Absorbing Markov chain are:

- At least, it has one absorbing state
- The absorption ends in an absorbing state with probability 1

In this work, the transition matrix was performed from the principal organs with higher probability for developing metastasis. However, for some organs, if the tumor is originated there or if it is developed elsewhere (first or secondary sites), do not evolve as metastasis from there. The absorbent states are organs that rarely metastasize, i.e. these are organs do not generate metastasis in the next step of the transition matrix. The Absorbing States of P are: **Bone (Bo)**, **Brain (Bra)**, **Liver (Li)**, **Peritoneum (Pe)**, **Adrenal Gland (A)** and **Skin/Muscle (SM)**.

IV. TRANSITION MATRIX FOR TERTIARY SITES (SECOND METASTASIS)

For the process to move from state i to state j in two steps, it must go through an intermediate state k . If a tumor in a secondary site spreads to a new organ (tertiary site), this will be labelled as X_2 . The probability of generate a new tumor in a tertiary site from a primary site is given by:

$$p_{ij}^{(2)} = P[X_2 = j | X_0 = i] = \sum_{k=1}^m p_{ik} \cdot p_{kj} \quad (4)$$

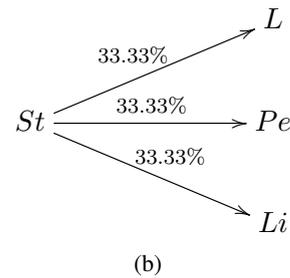
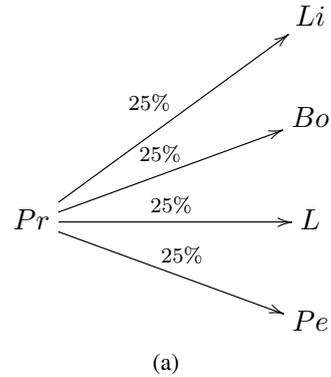


Fig. 3: Probabilities (in percentage) of metastasis in organs from Prostate (a) and Stomach (b) cancer respectively.

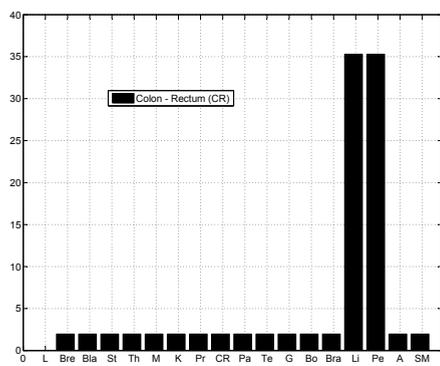
where $i, j, k = 1, 2, 3, \dots, m$ number of organs. Similarly Eq. 2, the new *transition matrix for Second Step* $P^{(2)}$ is built for males and this is given by:

$$P^{(2)} = [p_{ij}^{(2)}], \quad P^{(2)} \in \mathbb{R}^{m \times m} \quad (5)$$

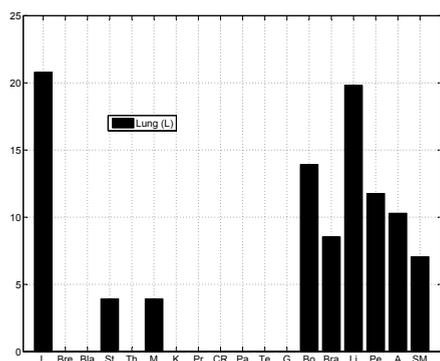
Eq. 5 gives information how to obtain a second metastasis from the original tumor going through the possible connections. Although the metastasis from metastasis is unlikely, some clinical evidence was found in cites [16], [17]. The matrix $P^{(2)}$ is shown Appendix B.

Therefore, $P^{(2)}$ allows to find the probabilities of metastasis in a tertiary site from a primary site. For sake of clarity, examples are shown in Fig. 4a and 4b.

A global analysis of the matrix $P^{(2)}$ shows that if the primary site is the Lung (L), absorbing



(a)



(b)

Fig. 4: Probabilities (in percentage) for tumors in tertiary site from (a) Colon/Rectum (*CR*) and (b) Lung (*L*).

states are the most probable tertiary sites as discussed in Sec. 3 (*Bo*, *Bra*, *Li*, *Pe*, *A* and *SM*). This remarks the role of Lung as the principal link between organs[18]. For other organs (disregarding the absorbing states), if the tumor is developed, there is some probability to generate metastasis in a tertiary site.

In sum, according with recent statistics[8], the principal tumors in the population are Lung (*L*) and Colon/Rectum (*CR*) tumor. In the *P* matrix can be observed the probabilities for evolving a tertiary site tumor from those

two. If Colon/Rectum tumor is a primary site, the principal tertiary sites are Liver (*Li*) and Peritoneum (*Pe*). And, if there is a Lung tumor, the principal tertiary sites are the absorbing states (*Bo*, *Bra*, *Li*, *Pe*, *A* and *SM*), as it was previously discussed. This can be visualized in the Fig. 5.

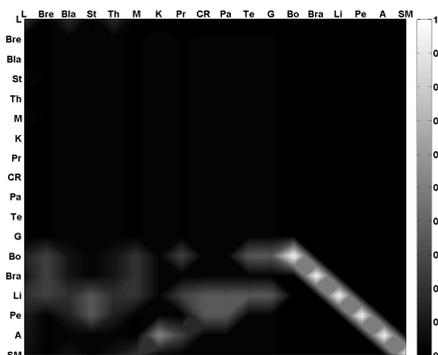


Fig. 5: Visualization of the transition matrix, in gray scale, for tertiary sites.

V. ANALYSIS OF THE EXPECTED NUMBER OF STEPS AND PROBABILITY OF ABSORPTION BY ABSORBING STATES

When the processes are absorbing, the number of steps before the system is absorbed, as well as, the probability of absorption of any absorbing state can be found. In order to find this process, each transition matrix will be represented in its canonical form[14], called *J*. It is composed by 4 sub-matrices: *N* (this sub-matrix contains the probabilities are moving from a non-absorbing state to another non-absorbing state), *A* (sub-matrix that contains the probabilities of going from a non-absorbing state to another absorbing state), *O* (zero sub-matrix) and *I* (identity sub-matrix).

$$J = \begin{pmatrix} N & A \\ O & I \end{pmatrix}$$

The matrices with smaller probability contain elements that originate *a* absorbing states and *n* non-absorbing states. There are $a + n = m$ states

of the system.

Let be the fundamental matrix $F = I + N + N^2 + \dots = (I - N)^{-1}$ [14]. We can calculate from a transient state the expected number of steps before being absorbed by an absorbing state. Let t_i be the expected number of steps before the chain is absorbed when this begins in a transient state i , and let \bar{t} be the column vector whose $i - th$ entry is t_i . Then, the vector \bar{t} can be estimated by the following expression[14]:

$$\bar{t} = F \cdot \bar{c} \tag{6}$$

where \bar{c} is vector whose entries are all one.

$$\bar{t} = \begin{matrix} L \\ Bre \\ Bla \\ St \\ Th \\ M \\ K \\ Pr \\ CR \\ Pa \\ Te \\ G \end{matrix} \begin{matrix} \text{steps} \\ \left[\begin{array}{c} 2.237 \\ 1.559 \\ 2.810 \\ 1.745 \\ 2.810 \\ 1.447 \\ 2.118 \\ 1.559 \\ 1.745 \\ 1.745 \\ 1.745 \\ 1.745 \end{array} \right] \end{matrix}$$

In \bar{t} are shown the tumors with more than one stage of metastasis (given the nearest integer, one stage or a step is the first metastasis in a secondary site, and two steps is the second metastasis in a tertiary site). Bladder and Thyroid have a higher number of steps, Lung and Kidney have the maximal steps around two, this coincides with the main trend of mortality in males due to these tumors[12], [21].

In addition, the probability of absorption of any non-absorbing state by any absorbing states can be calculated, and this is given by[14]:

$$Z = F \cdot A \tag{7}$$

	$Z =$					
	<i>Bo</i>	<i>Bra</i>	<i>Li</i>	<i>Pe</i>	<i>A</i>	<i>SM</i>
<i>L</i>	0.190	0.120	0.283	0.169	0.133	0.10
<i>Bre</i>	0.297	0.280	0.320	0.042	0.033	0.025
<i>Bla</i>	0.164	0.128	0.322	0.197	0.068	0.118
<i>St</i>	0.063	0.040	0.427	0.389	0.044	0.033
<i>Th</i>	0.164	0.128	0.322	0.197	0.068	0.118
<i>M</i>	0.238	0.224	0.256	0.033	0.026	0.220
<i>K</i>	0.095	0.060	0.141	0.084	0.566	0.050
<i>Pr</i>	0.297	0.030	0.320	0.042	0.283	0.025
<i>CR</i>	0.063	0.040	0.427	0.389	0.044	0.033
<i>Pa</i>	0.063	0.040	0.427	0.389	0.044	0.033
<i>Te</i>	0.063	0.040	0.427	0.389	0.044	0.033
<i>G</i>	0.063	0.040	0.427	0.389	0.044	0.033

Here, the matrix Z shows the probability that a specific organ (not belonging to the absorbing states) is absorbed by an absorbing specific organ. If we take as a reference the estimated sum of all elements of each column (i.e., each absorbing state), the main probabilities are Liver(*Li*) and Bones (*Bo*), following by Peritoneum (*Pe*) and Adrenal Gland (*A*).

VI. CONCLUSIONS

In order to search new ways to understand the metastasis process and its interactions among organs sites of possible metastasis, Absorbing Markov chains were used as a mathematical tool to achieve this goal. A characterization of the route of metastasis was developed. The Lung as the main connector between the primary site and the tertiary site, with defined probabilities in emphasized.

The graphs and their connections, in order to develop the transition matrices for the occurrence of tumors, are a good approximation to the reality. These matrices exhibit the connections and the existence of absorbing states in organs with lower probabilities (almost null) to generate metastasis ([19], [20]) in secondary sites, absorbing states represent organs that are not the source of metastasis (sponges as Newton calls in [6]).

By the analysis of the expected steps number and the probability of absorption by absorbing states, it is possible to predict the tertiary sites from the secondary sites[22] (or at least estimated

them). Furthermore, a quantized approximation of the transition matrices of second step $P^{(2)}$ can be obtained. It is a result useful for treatments and therapies given its predictive character. Also, we know that as we get more data on statistics of metastasis, our analysis will be more accurate. This can be through statistical methods or by predominant tumor cells (Stems, progenitors or differentiated) prevailing in each organ (or migrated from other organs such as CTCs). The latter is our immediate study object.

On the other hand, by the properties of Absorbing Markov chains, it was found that in no more than 2 steps (second metastasis in tertiary site) any absorbing states are reached: *Bo, Bra, Li, Pe, A* and *SM* as can be seen in the references [23], [24], [25], [26] and [27]. This also can be seen as a result from the point of view of our model, the main point is the fact that in 3 steps (P^3), we reach an absorbing state with a high probability (see Appendix C), where the sum of probabilities of each row, in the columns of absorbing organs, is near to 1.

$$\begin{matrix} L \\ Bre \\ Bla \\ St \\ Th \\ M \\ K \\ Pr \\ CR \\ Pa \\ Te \\ G \end{matrix} \left[\begin{array}{c} \sum_{abs=1}^6 p_{abs} \\ 0.845 \\ 0.928 \\ 0.790 \\ 0.905 \\ 0.790 \\ 0.943 \\ 0.857 \\ 0.928 \\ 0.905 \\ 0.905 \\ 0.905 \\ 0.905 \end{array} \right]$$

Where abs = Bo, Bra, Li, Pe, A and SM (The absorbing states).

This analysis is quite similar for females, taking into account the specific organs (Ovaries, Vagina and Uterus).

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APPENDIX

A. Matrix P : Probabilities to generate metastasis in a secondary site from a primary site.

	L	Bre	Bla	St	Th	M	K	Pr	CR	Pa	Te	G	Bo	Bra	Li	Pe	A	SM
L	0	$\frac{1}{17}$																
Bre	$\frac{1}{4}$	0	0	0	0	0	0	0	0	0	0	0	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	0	0	0
Bla	$\frac{1}{3}$	0	0	$\frac{1}{3}$	0	$\frac{1}{3}$	0	0	0	0	0	0	0	0	0	0	0	0
St	$\frac{1}{3}$	0	0	0	0	0	0	0	0	0	0	0	0	0	$\frac{1}{3}$	$\frac{1}{3}$	0	0
Th	$\frac{1}{3}$	0	0	$\frac{1}{3}$	0	$\frac{1}{3}$	0	0	0	0	0	0	0	0	0	0	0	0
M	$\frac{1}{5}$	0	0	0	0	0	0	0	0	0	0	0	$\frac{1}{5}$	$\frac{1}{5}$	$\frac{1}{5}$	0	0	$\frac{1}{5}$
K	$\frac{1}{2}$	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	$\frac{1}{2}$	0
Pr	$\frac{1}{4}$	0	0	0	0	0	0	0	0	0	0	0	$\frac{1}{4}$	0	$\frac{1}{4}$	0	$\frac{1}{4}$	0
CR	$\frac{1}{3}$	0	0	0	0	0	0	0	0	0	0	0	0	0	$\frac{1}{3}$	$\frac{1}{3}$	0	0
Pa	$\frac{1}{3}$	0	0	0	0	0	0	0	0	0	0	0	0	0	$\frac{1}{3}$	$\frac{1}{3}$	0	0
Te	$\frac{1}{3}$	0	0	0	0	0	0	0	0	0	0	0	$\frac{1}{3}$	0	$\frac{1}{3}$	0	0	0
G	$\frac{1}{3}$	0	0	0	0	0	0	0	0	0	0	0	$\frac{1}{3}$	0	$\frac{1}{3}$	0	0	0
Bo	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Bra	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Li	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Pe	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
A	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
SM	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

B. Matrix $P^{(2)}$: Probabilities to generate metastasis in a tertiary site from a primary site.

	L	Bre	Bla	St	Th	M	K	Pr	CR	Pa	Te	G	Bo	Bra	Li	Pe	A	SM
L	$\frac{53}{255}$	0	0	$\frac{2}{51}$	0	$\frac{2}{51}$	0	0	0	0	0	0	$\frac{71}{510}$	$\frac{29}{340}$	$\frac{101}{510}$	$\frac{2}{17}$	$\frac{7}{68}$	$\frac{6}{85}$
Bre	0	$\frac{1}{68}$	$\frac{9}{34}$	$\frac{9}{34}$	$\frac{9}{34}$	$\frac{1}{68}$	$\frac{1}{68}$	$\frac{1}{68}$										
Bla	$\frac{8}{45}$	$\frac{1}{51}$	$\frac{22}{255}$	$\frac{22}{255}$	$\frac{151}{765}$	$\frac{20}{153}$	$\frac{1}{51}$	$\frac{22}{255}$										
St	0	$\frac{1}{51}$	$\frac{1}{51}$	$\frac{6}{17}$	$\frac{6}{17}$	$\frac{1}{51}$	$\frac{1}{51}$											
Th	$\frac{8}{45}$	$\frac{1}{51}$	$\frac{22}{255}$	$\frac{22}{255}$	$\frac{151}{765}$	$\frac{20}{153}$	$\frac{1}{51}$	$\frac{22}{255}$										
M	0	$\frac{1}{85}$	$\frac{18}{85}$	$\frac{18}{85}$	$\frac{18}{85}$	$\frac{1}{85}$	$\frac{1}{85}$	$\frac{18}{85}$										
K	0	$\frac{1}{34}$	$\frac{1}{34}$	$\frac{1}{34}$	$\frac{1}{34}$	$\frac{1}{17}$	$\frac{1}{34}$											
Pr	0	$\frac{1}{68}$	$\frac{9}{34}$	$\frac{1}{68}$	$\frac{9}{34}$	$\frac{1}{68}$	$\frac{9}{34}$	$\frac{1}{68}$										
CR	0	$\frac{1}{51}$	$\frac{1}{51}$	$\frac{6}{17}$	$\frac{6}{17}$	$\frac{1}{51}$	$\frac{1}{51}$											
Pa	0	$\frac{1}{51}$	$\frac{1}{51}$	$\frac{6}{17}$	$\frac{6}{17}$	$\frac{1}{51}$	$\frac{1}{51}$											
Te	0	$\frac{1}{51}$	$\frac{6}{17}$	$\frac{1}{51}$	$\frac{6}{17}$	$\frac{1}{51}$	$\frac{1}{51}$	$\frac{1}{51}$										
G	0	$\frac{1}{51}$	$\frac{6}{17}$	$\frac{1}{51}$	$\frac{6}{17}$	$\frac{1}{51}$	$\frac{1}{51}$	$\frac{1}{51}$										
Bo	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Bra	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Li	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Pe	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
A	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
SM	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

C. Matrix $P^{(3)}$

$$P^{(3)} = \begin{matrix} & L & Bre & Bla & St & Th & M & K & Pr & CR & Pa & Te & G & Bo & Bra & Li & Pe & A & SM \\ \begin{matrix} L \\ Bre \\ Bla \\ St \\ Th \\ M \\ K \\ Pr \\ CR \\ Pa \\ Te \\ G \\ Bo \\ Bra \\ Li \\ Pe \\ A \\ SM \end{matrix} & \left[\begin{array}{cccccccccccccccccccc} \frac{16}{765} & \frac{5}{409} & \frac{18}{113} & \frac{55}{522} & \frac{43}{186} & \frac{1}{7} & \frac{41}{356} & \frac{33}{364} \\ \frac{49}{943} & 0 & 0 & \frac{1}{102} & 0 & \frac{1}{102} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{268}{941} & \frac{35}{129} & \frac{183}{611} & \frac{1}{34} & \frac{7}{272} & \frac{3}{170} \\ \frac{53}{765} & \frac{8}{765} & \frac{8}{765} & \frac{2}{85} & \frac{8}{765} & \frac{2}{85} & \frac{8}{765} & \frac{21}{170} & \frac{19}{180} & \frac{15}{59} & \frac{41}{255} & \frac{3}{67} & \frac{77}{765} \\ \frac{53}{765} & 0 & 0 & \frac{2}{153} & 0 & \frac{2}{153} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{20}{431} & \frac{23}{809} & \frac{244}{611} & \frac{19}{51} & \frac{7}{204} & \frac{2}{85} \\ \frac{53}{765} & \frac{8}{765} & \frac{8}{765} & \frac{2}{85} & \frac{8}{765} & \frac{2}{85} & \frac{8}{765} & \frac{21}{170} & \frac{19}{180} & \frac{15}{59} & \frac{41}{255} & \frac{3}{67} & \frac{77}{765} \\ \frac{18}{433} & 0 & 0 & \frac{2}{255} & 0 & \frac{2}{255} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{18}{79} & \frac{28}{129} & \frac{98}{409} & \frac{2}{85} & \frac{7}{340} & \frac{91}{425} \\ \frac{53}{510} & 0 & 0 & \frac{1}{51} & 0 & \frac{1}{51} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{41}{589} & \frac{29}{680} & \frac{91}{919} & \frac{1}{17} & \frac{75}{136} & \frac{3}{85} \\ \frac{49}{943} & 0 & 0 & \frac{1}{102} & 0 & \frac{1}{102} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{268}{941} & \frac{10}{469} & \frac{183}{611} & \frac{1}{34} & \frac{75}{272} & \frac{3}{170} \\ \frac{53}{765} & 0 & 0 & \frac{2}{153} & 0 & \frac{2}{153} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{20}{431} & \frac{23}{809} & \frac{244}{611} & \frac{19}{51} & \frac{7}{204} & \frac{2}{85} \\ \frac{53}{765} & 0 & 0 & \frac{2}{153} & 0 & \frac{2}{153} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{20}{431} & \frac{23}{809} & \frac{244}{611} & \frac{19}{51} & \frac{7}{204} & \frac{2}{85} \\ \frac{53}{765} & 0 & 0 & \frac{2}{153} & 0 & \frac{2}{153} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{20}{431} & \frac{23}{809} & \frac{244}{611} & \frac{19}{51} & \frac{7}{204} & \frac{2}{85} \\ \frac{53}{765} & 0 & 0 & \frac{2}{153} & 0 & \frac{2}{153} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{20}{431} & \frac{23}{809} & \frac{244}{611} & \frac{19}{51} & \frac{7}{204} & \frac{2}{85} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{array} \right] \end{matrix}$$