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Research Article


Analytical Expressions of the Markov Chain of K-Ras4B Protein within the Catalytic Environment and a New Markov-State Model

Orchidea Maria Lecian*

Sapienza University of Rome, Rome, Italy

*Correspondence: Orchidea Maria Lecian, Sapienza University of Rome, Rome, Italy, Email: orchideamaria.lecian@uniroma1.it


Abstract

The finite Markov chain to which there correspond the qualities of the conformational dynamics of the K-Ras4B proteins in the catalytic reaction is written. The corresponding Markov-States models are studied.

The properties of the K-Ras4B processes Markov chain allow one to define a new two-state MSM for the analytical description of the final-state transition. The time evolution of the eigenvalue corresponding to the final-state transition in the Galerkin description is written.

The tools for the analytical calculations of the relative error are therefore prepared.

New analytical formulations of the time evolution of the eigenvalue corresponding to the final-state transition are newly written from the experimental data and from the properties of the lag time in shaping the discretization error. The features of the discretization error are newly studied. A comparison with the experimental data is proposed.

Introduction

The roles of Ras proteins in transduction pathways and in the subsequent processes are investigated within the framework of oncogenesis in [1].

Further modalities of different K-Ras proteins and environments can be gained insight about from [2], in which the dynamics of the lipids membranes are analyzed within a Hidden-Markov-State Model from [3], and that of biomimetic membranes in [4].

The catalysis properties of the Ras proteins were studied in [5,6]. Ras proteins are used in anticancer drug design [7,8] clinical study for drug discovery is reported to be conducted in [9].

The role of the conformational dynamics in pharmaceutical uses was envisaged in [10].

The catalysis setting examined is one in which the 'intrinsically-disordered Hyper-viable region' (HVR) interacts with the catalytic domain at the 'effector' binding region (as an 'auto-inhibiting' state).

Large-scale conformational transitions of the HVR are studied, from the intrinsically disordered conformation to the ordered one.

The description of the path crucially involves 'key' conformal substrates along the transition pathways; interactions between the HVR and the catalytic domain are considered as being possible.

The states hypothesized as being two possible Markov-States-Model (MSM) states of the K-Ras4B processes were described in [1] after the time-scale test. The description of the 'disordered' part of the dynamical is issued from [11]. Accordingly, the activity at the atomic level gained insight after the analysis of the pathways.

In the present work, the qualities of the time evolution of the K-Ras4B are analytically investigated.

The finite Markov chain corresponding to the K-Ras4B processes is defined after newly spelling out the fundamental matrix and the probability matrix. The MSMs corresponding to the K-Ras4B processes are investigated. A new two-states MSM is here implemented, in order to specify the qualities of the final-state transition, which consists of the M_4 - M_5 MSM: within this



new analysis, the time evolution of the eigenvalue in the Galerkin description is spelled out; moreover, new analytical expressions are written after the properties of the MFPT and of the lag time. This way, the new tools to spell the relative error and the discretization error are introduced. A comparison with the experimental data available from [1] is proposed [12].

The paper is organized as follows

The qualities of the K-RAS proteins are briefly recalled in Section 2. The Markov free-energy-barrier landscape is sketched in Section 3.

The Markov chain originating the Markov states Models is newly found: the fundamental matrix and the probability matrix are newly analytically written in Section 4.

The states of MSM's landscapes are newly analyzed in Section 5; more in detail, the M_1 - M_2 - M_3 - M_4 - M_5 MSM is discussed in Section 6, and the qualities of the M_1 - M_3 - M_4 - M_5 MSM are newly spelled out in Section 7.

In Section 8, a new two-states MSM is constructed: the new M_4 - M_5 model is set after the Mean first passage time (MFPT) of the transition in order for the statistical tools to be applied, and the expression of the time evolution of the pertinent eigenvalue in the Galerkin description is spelled.

New expressions of the time evolution of the eigenvalue corresponding to the final-state transition are calculated in Section 9 according to the properties of the MFPT and to those of the lag time, which are newly made use of in the analysis.

The juxtaposition of the perspective studies is presented in Section 11. A comparison with the experimental data is proposed.

Introduction to K-RAS structure and to their dynamics

The qualities of the K-RAS signal-transducer proteins are recapitulated in [13]; here the dynamics of the K-RAS are reviewed at the atom-lengthscale level and at the conformational-dynamics examination.

The use of the Markov-State Models (MSM) is based on the long time scale statistical dynamics according to the transition probabilities of the protein conformational dynamics explained in [14]: as a result, from [13], 7 metastable states are outlined to be due to sub-states of the switches.

Furthermore, the several K-RAS types of proteins exhibit different behaviors with respect to the metastable states: accordingly, the shift in the K-RAS dynamics is reviewed to happen in an allosteric way.

The differences between the oncogenic K-RAS mutants are juxtaposed in [15-17].

The different binding profiles can be compared within [15,18].

The results interpreted from molecular dynamics simulations

might allow one to infer that different mutants have different dynamics [19-21] according to the different Markov landscapes.

The Markov landscape

The data available from the experiment allow one to make hypotheses about the Markov landscapes of the MSM's fitting the process.

One instance consists of a 4 - state landscape, in which the dynamics take place. More in detail, the states are named M_1 , M_3 , M_4 , M_5 . The second instance is a 5-state landscape, whose states are named M_1 , M_2 , M_3 , M_4 , and M_5 .

The experimental comparison is achieved, according to the investigation of the passage through the state M_2 .

The Markov chain

The Markov chain M originating the process is here newly studied as one composed of 5 states which are analytically written after the partitions of the available portion of the Markov landscape, which are schematised as step functions (on which the path integrals will be calculated).

The first-hitting-time matrix function is spelled from [1].

The fundamental matrix

The fundamental matrix \hat{Q} of the Markov chain M pertinent to the considered process of transitions is here newly written as

$$\hat{Q} = \begin{bmatrix} -q_{1 \rightarrow 2} - q_{1 \rightarrow 3} & q_{1 \rightarrow 2} & q_{1 \rightarrow 3} & 0 & 0 \\ q_{2 \rightarrow 1} & -q_{2 \rightarrow 1} - q_{2 \rightarrow 3} & q_{2 \rightarrow 3} & 0 & 0 \\ 0 & 0 & 0 & q_{3 \rightarrow 4} & 0 \\ 0 & 0 & 0 & 0 & q_{4 \rightarrow 5} \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

The diagonal entries are controlled to be non-positive.

The probability matrix

The probability matrix \hat{P} is defined as

$$\hat{P}(t) \equiv e^{\hat{Q}t} \quad (1)$$

and is here newly written as

$$\hat{P} = \begin{bmatrix} 1 - p_{1 \rightarrow 2} - p_{1 \rightarrow 3} & p_{1 \rightarrow 2} & p_{1 \rightarrow 3} & 0 & 0 \\ p_{2 \rightarrow 1} & -p_{2 \rightarrow 1} - p_{2 \rightarrow 3} & p_{2 \rightarrow 3} & 0 & 0 \\ 0 & 0 & 1 - p_{3 \rightarrow 4} & p_{3 \rightarrow 4} & 0 \\ 0 & 0 & 0 & 1 - p_{4 \rightarrow 5} & p_{4 \rightarrow 5} \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

In the probability matrix, each row is controlled to be summed as 1.

The MSM from the experimental data

The processes $M_1 \rightarrow M_3$ and $M_2 \rightarrow M_3$ are irreversible; thus,

the corresponding entries of the probability matrix are set at $p_{3 \rightarrow 1}$ and $p_{3 \rightarrow 2}$ are set as vanishing; the corresponding modification has to be appointed on the fundamental matrix of the Markov chain as well.

The processes $M_3 \rightarrow M_4$ and $M_4 \rightarrow M_5$ are described as irreversible; therefore, the values of the following entries of the probability matrix are set at $1 - p_{34} \rightarrow 0$ and $1 - p_{45} = 0$.

Because the system is always found to be at the final state M_5 , then $p_{55} = 1$. The pertinent entries of the matrices are therefore calculated accordingly.

The M_1 - M_2 - M_3 - M_4 - M_5 MSM

The M_1 - M_2 - M_3 - M_4 - M_5 MSM is one containing the five states M_1 , M_2 , M_3 , M_4 , and M_5 , which are here newly issued from the Markov chain M. The transition probabilities are those evaluated from the probability matrix P^\wedge .

The M_1 - M_3 - M_4 - M_5 MSM

The Markov chain of this model is here newly set as one for which the transition probabilities pertinent to the state M_2 are set to vanish.

The M_1 - M_3 - M_4 - M_5 MSM is here newly written as one containing the four states M_1 , M_3 , M_4 , M_5 issued from the Markov chain M; this MSM is one obtained after projecting out the vector pertinent to the state M_2 out from the Banach space B of M by means of a projector operator; the corresponding Banach space is therefore here found to be one dimension less than that of the M_1 - M_2 - M_3 - M_4 - M_5 scheme.

The new projected probability matrix P^\sim is therefore newly written as

$$\hat{P} = \begin{bmatrix} 1 - p_{1 \rightarrow 3} & p_{1 \rightarrow 3} & 0 & 0 \\ 0 & 1 - p_{3 \rightarrow 4} & p_{3 \rightarrow 4} & 0 \\ 0 & 0 & 1 - p_{4 \rightarrow 5} & p_{4 \rightarrow 5} \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

Similar to the previous analysis, the transitions $M_3 \rightarrow M_4$ and $M_4 \rightarrow M_5$ are experimentally described as irreversible: for this reason, the corresponding probabilities have to be set accordingly.

The new M_4 - M_5 MSM

The transition $M_4 \rightarrow M_5$ is experimentally validated as irreversible from [1]; it is therefore possible to define the 2 - states MSM constituted of the two states M_4 and M_5 .

The time evolution of the eigenvalue is calculated as the total reward of the path integral (which describes the path followed in the memory-less case). The time evolution of the eigenvalue at the time τ is a function of the eigenvalue shift evaluated at the time $t + \tau$ (and of the time-evolved eigenvalue). The time evolution of the eigenvalue is calculated as the Laplace kernel from [22] and the

references therein as one with Radon measure as.

$$\tilde{\lambda}_\tau = \int_0^\infty e^{-\theta\Lambda(t-\tau)} e^{-\theta\tilde{\delta}\Lambda(t-\tau)} d\theta = \frac{1}{\Lambda(t-\tau) + \tilde{\delta}\Lambda} \quad (2)$$

Where the auxiliary time variable is wanted not to coincide with the exit time (which is implicit for the final state M_5): in Eq. (2),

9 New analytical calculations about the time evolution of the final state

It is now possible to calculate the time evolution of the M_5 eigenvalue immediately after the time at which the state M_5 starts being populated after choosing the lower integration extremum as the time immediately after the (mean) first passage time (MFPT) of the transition $M_4 \rightarrow M_5$.

This way, the time evolution of the eigenvalue $\lambda_{5,\tau}^\sim$ is newly obtained after specifying Eq. (2) as

$$\tilde{\lambda}_\tau = \int_{58.55+\epsilon}^\infty e^{-\theta\Lambda(t-\tau)} e^{-\theta\tilde{\delta}\Lambda(t-\tau)} d\theta = \frac{1}{\Lambda(t-\tau) + \tilde{\delta}\Lambda} e^{-(55.55+\epsilon)(\Lambda(t-\tau) + \tilde{\delta}\Lambda)}. \quad (3)$$

About the discretization error

It is possible to apply here the ingredients from [23], after which it is possible to pose that the time evolution of the eigenvalue at the time τ be a function of the eigenvalue shift evaluated at the time $t + \tau$ only: this way, the time evolution of the eigenvalue λ_τ^\sim is newly obtained after specifying Eq. (2) as

$$\tilde{\lambda}_\tau = \int_{58.55+\epsilon}^\infty e^{-\theta\Lambda(\tau)} e^{-\theta\tilde{\delta}\Lambda} d\theta = \frac{1}{\Lambda(\tau) + \tilde{\delta}\Lambda} e^{-(55.55+\epsilon)(\Lambda(\tau) + \tilde{\delta}\Lambda)}. \quad (4)$$

Discussion

The description of the Markov landscape as far as the free-energy barriers are concerned was further investigated in [24] and in [25].

The calculation of the path integral (from which the total reward is considered) is here not possible yet, according to the experimental data from [1], from which the $q_{i,j}$ elements are not spelled out (nor are those of the transition matrix, from which the Q^\wedge matrix can be extracted after the Kolmogorov equation); nevertheless, the calculations from its reward allow one to pose new further estimates. For the presented purposes, the new two-states MSM is constructed from the states M_4 and M_5 , from which the time evolution of the eigenvalue pertinent to the final-state transition is analytically calculated in the Galerkin description; furthermore, the new estimates are issued from the experimental data available from [1] for the new definitions of the time evolution of the wanted eigenvalues, for which the relative error and the discretization error acquire their physical characterization.

As from [23], the discretization error is expected to increase monotonically with the lag time. As from the accurate estimates from [1], the system was demonstrated to be a Markovian one; in the present work, the detailed specifications of [23] can be in this case also applied, after which the calculation of the discretization error

is apt to satisfy the standards requested *ibidem*. The present work is aimed at analyzing the properties of the dynamics of the K-Ras4B proteins within the framework of the catalytic environment by means of the techniques of the MSM. Different interactions of the proteins, i.e. such as those with the lipids membranes, are described within the framework of a Hidden Markov-State Model. In both cases, a dynamical pattern is individuated among the three first states.

The novelty of the approach here presented is aimed at recovering the items of information about the catalytic mechanism by taking into account the irreversible transition from the penultimate state to the final state. For this purpose, a new two-state MSM was built, which is issued from the Markov chain of K-RAS4B. It is therefore possible to recover the qualities of the eigenvalue of the final transition in the Galerkin representation.

According to this representation, it is possible to retrieve the decay constant and the implied time scale in an analytical manner.

The relative error and the discretization error can be newly analytically calculated according to the qualities of the eigenvalue.

The comparison with the time evolution of the discretization error is therefore newly set.

Comparisons and perspective studies

In [26], the experimental data are scanned, to focus on the inhibition mechanisms of K-RAS(G12D) and its analogs: computer simulations are used to study the conformational space for the cluster analysis by means of a twelve-states MSM. The applications are envisaged to provide guidance for the design of new small molecule inhibitors and to project drugs against K-RAS in general. The analysis of [26,27] demonstrates that there are two clusters within the twelve-state MSM among which the experimental transition probability is high, i.e. one of the transitions $C_{10} \rightarrow C_{12}$, i.e. the state C_{11} is considered as not playing a strong role; according to this analysis, it is reasonable to newly postulate a Hidden Markov-State Model which comprehends only the two states, and to further implement the techniques developed of the two-states MSM.

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