

## ***Helicobacter pylori* leads to the Activation of Host Cell Intrinsic P53 Network Via DNA Damage: A Deterministic Model**

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### **ABSTRACT**

*Helicobacter pylori* (*H. pylori*) bacterium is widely studied risk factor of gastric cancer. The mechanism by which *H. pylori* induces gastric carcinogenesis, has been studied by various researcher. However, a molecular level mechanism by which *H. pylori* enters into the cells causes p53 modulation leads to stress and gastric cancer developments, is still an open question. In the present studied we developed p53-ROS-*H. pylori* model integrated deterministic model to show the molecular level interaction between p53 proteins network and *H. pylori* bacterium via reactive oxygen species. The interactions among p53 network proteins, reactive oxygen species and *H. pylori* are described by system of a set of ordinary differential equations. The rate of the reaction has been set by using pervious experimental and theoretical works. These sets of differential equations further numerically solved by using standard Runge-Kutta fourth order method at high computational cost. Numerical simulation results showed that as the accumulation of *H. pylori* ( $kHP < 0-0.5 >$ ) in the cells increases, the instability of p53 network systems are also increase. Various phases of the system have been observed viz normal phase, stable to damp phase, damped to stable phase and stationary phase. These phases correspond to various stages of cell cycle. The present model clarifies the molecular level interactions between *H. pylori* via reactive oxygen species. This model suggests that as the accumulation of *H. pylori* reaches at a particular threshold value, it leads to the cancerous progression. The suggested model will be very useful to understand the temporal dynamics of gastric cancer progression due to *H. pylori* bacterium. Further, study is needed in realistic environment.

**KEY WORDS:** HELICOBACTER PYLORY, P53, GASTRIC CANCER, DNA DAMAGE, TEMPORAL DYNAMICS.

### **ARTICLE INFORMATION**

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## INTRODUCTION

The expression of p53 tumor suppressor protein in the cell is reported as marker of the most of the cancer (Blagih et al., 2020). It acts as a key regulator in the cellular network and response to a variety of cellular stress, including DNA damage, hypoxia, nucleotide depletion, nitric oxide and aberrant proliferative signals (such as oncogene activation) (Moll and Petrenko, 2003). But in most cancerous cells, p53 tumor suppressor signaling pathway usually found in inactivated condition (Blagih et al., 2020). In normal cells, stress induced p53 leads to the participation in various key cellular processes, such as, cell-cycle arrest, senescence and most importantly tumor clearance to prevent cancer cell formation (Leeuwen, 2020, Zambetti, 2007). Moreover, it is reported that, activated p53 protein safeguards the organism against the propagation of cells that carry damaged DNA with potentially oncogenic mutations (Moll and Petrenko, 2003).

p53 act as transcription factor of MDM2 protein. Moreover, MDM2 act as negative feedback regulator of p53 protein which is also considered as an effective approach in cancer therapy (Leeuwen, 2020, Michael and Oren, 2003). MDM2 physically blocking its ability binding itself to p53 leads to the transactivation of p53 gene expression, and stimulating its degradation (Fang et al., 2000). Further, the interaction of N-terminal domain of MDM2 with transactivation domain of p53 (p53TAD) performs a significant role in the regulation of the G1 checkpoint of the cell cycle and cell function (Boyd et al., 2000). ROS (Reactive oxygen species) are chemically reactive molecules containing oxygen ions and peroxides (Amendola et al., 2013). They are synthesized from normal metabolism of oxygen as a natural byproduct and play important roles in cell signaling and homeostasis (Devasagayam et al., 2004; Rowe et al., 2008 and Poetsch, 2020).

However, ROS level inside cell can be elevated by UV irradiation or heat exposure which can drive the cell at different stress states (Devasagayam et al., 2004) High level of ROS can promote DNA damage, and may probably lead the cell to mutagenesis, carcinogenesis and aging (Poetsch, 2020, Amendola et al., 2013; Rowe et al., 2008; Proctor and Gray, 2010). *H. pylori* is a structurally spiral shaped bacterium. It generally present in digestive tract of the human. It is reported that in developing country children are commonly infected by *H. pylori* (Horvat et al., 2018; Kakelar et al., 2019, Choi, et. al, 2020).

Studies suggests that control of *H. pylori* leads to the control of gastric cancer (Ford et al., 2020, Hu et al., 2020; Sablet et al., 2011). The inclusion of *H. pylori* in the host cells increases the production of ROS, which further leads to the suppression of the endogenous level of p53 protein via DNA damage and represses to apoptosis in human gastric cells (Handa et al. 2011; Polk and Peek, 2010). Various studies have been performed to understand the mechanism by which *H. pylori* induces

gastric carcinogenesis (Wang et al., 2020, Handa et al., 2011, Achanta et al., 2004). However, how the dynamical behaviour of p53 protein changes at molecular level due to *H. pylori* via reactive oxygen species, is still an open question. In the present study, we try to answer these fundamental questions based on basic deterministic model.

## MATERIAL AND METHODS

p53-MDM2-*H. pylori* model.- The model we consider (Fig. 1) is integration of p53-Mdm2 regulatory network (Proctor and Gray, 2008) with stress inducers ROS via DNA damage (Rowe et al., 2008) and *H. pylori* (Handa et al., 2011). In this model we assume that *H. pylori* are supposed to be constantly entered in the nucleus after infection. ROS synthesis due to *H. pylori* is assumed to occur with a rate of  $k_{12}$ . This ROS synthesis triggers DNA damage with a rate of  $k_{14}$  (Rowe et al., 2008). Then this DNA damage leads to the activation of ARF with a rate  $k_{16}$  (Lee et al., 2005) followed by the degradation of ARF with a rate of  $k_{17}$ . Further, the activated ARF protein binds to MDM2 with a rate of  $k_{18}$  to control ubiquitination of p53 (Zhang and Xiong, 2001) The ARF and MDM2 interaction results into to the formation of ARF\_MDM2 complex (Khan et al., 2004).

The formation of ARF\_MDM2 complex reduces the concentration level of MDM2 in the system which in turn alters the behaviour of p53 (Khan et al., 2004). On the other hand, dissociation of ARF\_MDM2 complex with a rate  $k_{19}$  helps the degradation of MDM2 population and recruit activated ARF. The synthesis of p53 takes place through transcription of p53\_mRNA with a rate  $k_2$ . Further, this p53 synthesis depends on the available p53\_mRNA concentration level. At normal condition p53 is generally bound to MDM2 with a rate  $k_8$  recruiting a complex p53\_MDM2 and after which the dissociation of the complex ubiquitinates p53 with a rate  $k_9$  and MDM2 with a rate  $k_{12}$  (Zatorsky et al., 2006) exhibiting oscillatory behavior of p53 in the model. Further, rate of MDM2 transcription by p53 via production of MDM2\_mRNA, at  $k_5$  (Proctor and Gray, 2008).

Hence, the MDM2\_mRNA provides intermediary link between p53 and MDM2. The self ubiquitination of MDM2\_mRNA is assumed to be with a rate  $k_7$ . MDM2\_mRNA synthesize MDM2 protein with a rate  $k_6$ . The self ubiquitination of MDM2 is assumed to be with a rate  $k_{11}$ . The molecular species involved in this model are listed in Table 1, and the biochemical reaction channels involved in the model network with their descriptions, kinetic laws and values of the rate constants used in our simulations are given in Table 2. The model biochemical network (Fig. 1) described by the twenty two reaction channels (Table 2) can be described by the following coupled ordinary differential equations (ODE) using Mass action law of chemical kinetics,

$$\frac{dx_1}{dt} = k_2 * x_4 - k_8 * x_1 * x_2 + k_{10} * x_5$$

$$\frac{dx_2}{dt} = k_6 * x_3 - k_8 * x_1 * x_2 + k_9 * x_5 + k_{10} * x_5 - k_{11} * x_2 - k_{18} * x_2 * x_8$$

$$\frac{dx_3}{dt} = k_5 * x_1 - k_7 * x_3$$

$$\frac{dx_4}{dt} = -k_3 - k_4 * x_4$$

$$\frac{dx_5}{dt} = k_8 * x_2 * x_1 - k_9 * x_5 - k_{10} * x_5$$

$$\frac{dx_6}{dt} = k_{12} * x_{10} - k_{13} * x_6 - k_{14} * x_6$$

$$\frac{dx_7}{dt} = k_{14} * x_6 - k_{15} * x_7$$

$$\frac{dx_8}{dt} = k_{16} * x_7 - k_{17} * x_8 - k_{18} * x_8 * x_2 + k_{19} * x_9$$

$$\frac{dx_9}{dt} = k_{18} * x_8 * x_2 - k_{19} * x_9 \quad \frac{dx_{10}}{dt} = k_1 - k_{20} * x_{10} - k_{12} * x_{10}$$

The set of ODEs can be written in compact form as in the following,

$$\frac{dx(t)}{dt} = F(x_1, x_2, \dots, x_N) \quad \text{Where } F = [F_1, F_2, \dots, F_N]^T \text{ is the}$$

functional vector.

The time evolution of the state vector  $\vec{x}(t)$  can be obtained by numerically solving the non-linear coupled differential equations (1)-(11) using standard 4th order Runge-Kutta algorithm for numerical integration (Press, 1992). Consider the state of the system be described by a state vector given by  $\vec{x}(t) = [x_1(t), x_2(t), \dots, x_N(t)]^T$ , where,  $\{x\}$  is the set of concentrations of the respective molecular species,  $N=10$  and  $T$  is the transpose of the vector. The model biochemical network (Fig. 1) described by the twenty reaction channels (Table 2) can be described by the following coupled ordinary differential equations (ODE) using Mass action law of chemical kinetics,

$$\frac{dx_i(t)}{dt} = F_i[x_1(t), x_2(t), \dots, x_N(t)]$$

where,  $i=1,2,\dots,N$  and  $F_i$  is the  $i$ th function whose form is given in table. The non-linear coupled  $N$  ODEs of p53-MDM2-*H. pylori* model are solved using 4th order Runge-Kutta method which is the standard algorithm for numerical integration (Press, 1992) to find the dynamics of the system variables. The simulation is done for 10 days using the parameter values given in Table 2 and starting from an initial condition.

## RESULTS AND DISCUSSION

**Role of *H. pylori* on p53 dynamics:** The impact of *H. pylori* on p53 was studied by keeping fixed  $k_6=0.0001$  and allowing to change the values of  $k_{10}$  (Fig. 2). We got three different states namely stable, damped with sustain oscillation and again stable state of p53 driven by *H.*

*pylori* (Fig. 2). The small values of  $k_{10}$  ( $k_{10} < 0.001$ ) could not able to provide significant stress to p53 dynamics, and maintains at stabilized state (Fig. 2 E). The further increase in  $k_{10}$  values ( $0.001 < k_{10} < 0.1$ ) Fig. 2 A). This suggests that the increase in concentration of *H. pylori* ( $k_{10}$  corresponds to kHP) in the system drives the system at various stress states, lowering p53 concentration level (Wei et. al., 2010; Polk and Peek, 2010; Handa et. al., 2011). Moreover suggests that extreme values of  $k_{ROS}$  may cause very high DNA damage, such that the damage could not able to be repaired back, which could be the condition of apoptotic phase. The excess kHP values induce lowering of p53 concentration level even below normal stabilized p53 state indicating the possibility of switching stress state to cancerous state (Handa et. al., 2011).

Table 1. List of molecular species

S.No.	Species Name	Description	Notation
1.	p53	Unbounded p53 protein	x_1
2.	MDM2	Unbounded Mdm2 protein	x_2
3.	MDM2_mRNA	Mdm2 messenger mRNA	x_3
4.	p53_mRNA	p53 messenger mRNA	x_4
5.	p53_MDM2	Mdm2 with p53 complex	x_5
6.	ROS	Reactive Oxygen Species	x_6
7.	Dam_DNA	Damage DNA	x_7
8.	ARF	Alternative Reading Frame protein	x_8
9.	ARF_MDM2	ARF and Mdm2 complex	x_9
10.	HP	<i>Helicobacter pylori</i> factor	x_10

**Modulation of p53 dynamics by *H. pylori*:** The impact of *H. pylori* on the amplitude and time period of p53 dynamics is studied (Fig. 3) in order to understand modulation of p53 dynamics driven by stress inducer. The impact of  $k_{HP}$  on amplitude and time period of p53 dynamics is shown (Fig. 3). The lower values in  $k_{HP}$  could not able to make significant change in amplitude of p53 dynamics, and maintains at stable state with high value of constant p53 amplitude (Fig. 3). Further increase in  $k_{HP}$  drives the p53 amplitude to decrease monotonically, and then reach a stable state with minimum amplitude. The behaviour of the time period  $T_{p53}$  as a function of  $k_{HP}$  shows three regimes, stable, monotonically decreased with increase in  $k_{HP}$  and stable state again. However the different behaviour i.e. the decrease in  $A_{p53}$  as increase in  $k_{HP}$  may trigger cancer state from stress condition.

**Co-existence of states:** The phase transition like behaviour of the system dynamics induced by *H. pylori* concentrations available in the system can be well characterized by analyzing the nature of transition time of the p53 dynamics. We define  $T_{1s}$  to be the transition time below ( $<T_{1s}$ ) which the dynamics shows stable state (does not show any oscillation) and above which the dynamics shows oscillatory behaviour. We further define second transition time,  $T_{ds}$  which separates increasing damped and sustain oscillations (Fig. 2). Similarly,  $T_{sd}$

and  $T_{2s}$  are taken as transition times separating sustain and damped oscillation, and damped oscillation and stabilized state. We then calculated  $T_{1s}$ ,  $T_{ds}$ ,  $T_{sd}$  and  $T_{2s}$  as a function of kHP (Fig. 4 upper panel) where the regimes for  $T < T_{1s}$  and  $T < T_{2s}$  corresponds to stabilized states, regimes between  $T_{ds} < T < T_{1s}$  and  $T_{2s} < T < T_{sd}$  corresponds to damped states and  $T_{sd} < T < T_{ds}$  indicates the sustain oscillation state regime.

Table 2. List of chemical reaction, Kinetic Laws and their rate constant

S. No.	Name of the process	Kinetic Law	Rate Constant	References
1.	Inclusion of <i>Helicobacter pylori</i>	$k_1$	$1*10^{-4}sec^{-1}$	(Handa et. al., 2011)
2.	p53 mRNA translati	$k_2x_4$	$8*10^{-2}sec^{-1}$	(Moll and Petrenko, 2003; Proctor and Gray, 2008)
3.	p53 mRNA synthesis	$k_3$	$1*10^{-3}sec^{-1}$	(Moll and Petrenko, 2003; Proctor and Gray, 2008)
4.	p53 mRNA degradation	$k_2x_4$	$1*10^{-4}sec^{-1}$	(Moll and Petrenko, 2003; Proctor and Gray, 2008)
5.	Mdm2 mRNA synthesis	$k_5x_1$	$1*10^{-4}sec^{-1}$	(Moll and Petrenko, 2003; Proctor and Gray, 2008)
6.	Mdm2 synthesis	$k_6x_3$	$495*10^{-5}sec^{-1}$	Moll and Petrenko, 2003; Proctor and Gray, 2008)
7.	Mdm2 mRNA degradation	$k_7x_3$	$1*10^{-4}sec^{-1}$	Moll and Petrenko, 2003; Proctor and Gray, 2008)
8.	p53 Mdm2 complex forma-tion	$k_8x_1x_2$	$1155*10^{-5}sec^{-1}$	Moll and Petrenko, 2003; Proctor and Gray, 2008)
9.	Mdm2 creation	$k_9x_5$	$825*10^{-5}sec^{-1}$	Moll and Petrenko, 2003; Proctor and Gray, 2008)
10.	Dissociation of p53 Mdm2 complex	$k_{10}x_5$	$1155*10^{-5}sec^{-1}$	Moll and Petrenko, 2003; Proctor and Gray, 2008)
11.	Mdm2 degradation	$k_{11}x_2$	$433*10^{-5}sec^{-1}$	Moll and Petrenko, 2003; Proctor and Gray, 2008)
12.	ROS formation	$k_{22}x_{10}$	$1*10^{-4}sec^{-1}$	(Proctor and Gray, 2010; Proctor and Gray, 2008)
13.	Degradation of ROS	$k_{18}x_6$	$2*10^{-2}sec^{-1}$	(Proctor and Gray, 2010; Proctor and Gray, 2008)
14.	Initiation of DNA damage	$k_{14}x_6$	$2*10^{-2}sec^{-1}$	(Proctor and Gray, 2010; Proctor and Gray, 2008)
15.	DNA repair	$k_{15}x_7$	$2*10^{-5}sec^{-1}$	(Proctor and Gray, 2010; Proctor and Gray, 2008)
16.	Activation of ARF	$k_{16}x_7$	$33*10^{-5}sec^{-1}$	Zhang and Xiong, 2001; Proctor and Gray, 2008; Khan et. al., 2004)
17.	Degradation of ARF	$k_{17}x_8$	$1*10^{-4}sec^{-1}$	(Zhang and Xiong, 2001; Proctor and Gray, 2008; Khan et. al., 2004)
18.	ARF Mdm2 complex for-mation	$k_{18}x_8x_2$	$1*10^{-2}sec^{-1}$	(Zhang and Xiong, 2001; Proctor and Gray, 2008; Khan et. al., 2004)
19.	Dissociation of ARF Mdm2 complex	$k_{19}x_9$	$1*10^{-3}sec^{-1}$	(Zhang and Xiong, 2001; Proctor and Gray, 2008; Khan et. al., 2004)
20.	Degradation of Micro RNA	$k_{20}x_{10}$	$5*10^{-2}sec^{-1}$	(Handa et. al., 2011)



Figure 1: A schematic diagram of p53-Mdm2-*H. pylori* network model.

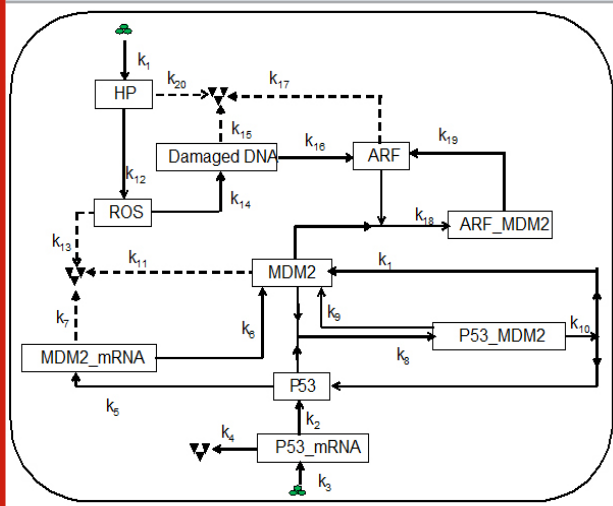
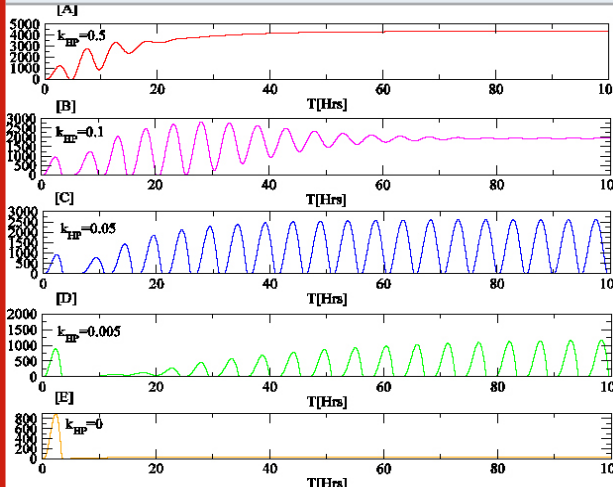


Figure 2: The p53 temporal behaviour when *H. pylori* act as a stress inducer



The co-existence of the four states can be obtained in the case of *H. pylori* induced p53 dynamics. Within this co-existence regime, the regions of damped, sustain and stabilized states are observed (Fig. 4). The results indicate that there is a certain range of  $k_{HP}$  (region bounded by two lines) where one can find the four states together including two stable states for any value of  $k_{HP}$  (Fig. 4). This means that for any concentration of ROS which is due to *H. pylori* in the system corresponding to any values within this range, the p53 dynamics will stay stable for some interval of time, then it will start activated to reach maximum activation within certain interval of time and after sometime it will stay stable again. In the other regimes, at most we can find three states. This co-existence of the states indicate that exposure of the system to constant *H. pylori* concentration can drive the system from normal to stress and then to apoptosis.

Figure 3: A comparative plot for the amplitude versus  $k_{HP}$  and the time period variation versus  $k_{HP}$ .

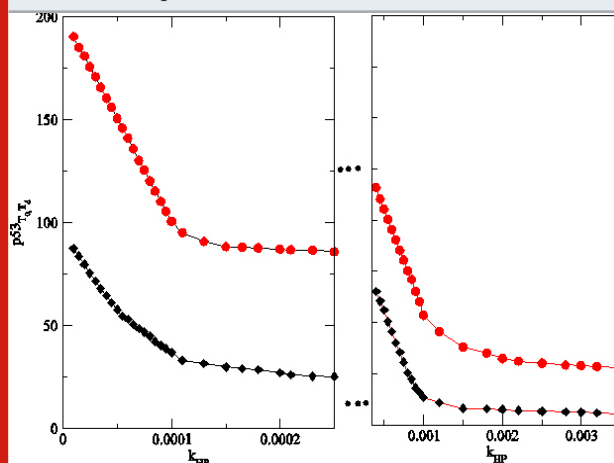
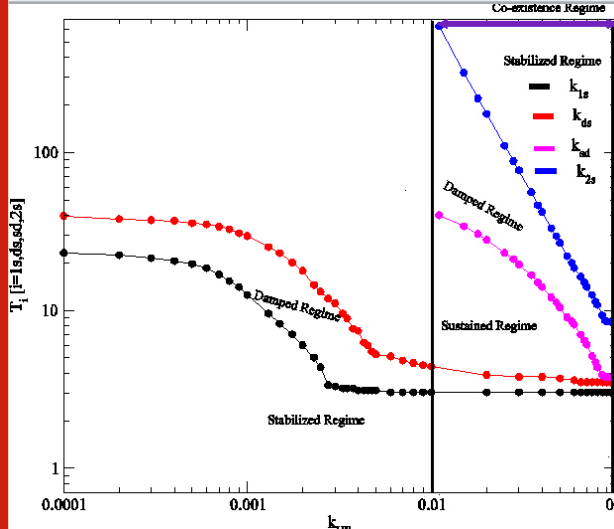


Figure 4: A phase diagram showing impact of  $k_{HP}$  on stability of p53 protein



### CONCLUSION

The variation in concentration of reactive oxygen species in cellular system triggers to the changes in the p53 dynamics (various stress states). Further, the introduction *H. pylori* to the system shows inhibitory effect on p53 production and switching of stress states by varying *H. pylori* concentration. Present model suggests that *H. pylori* accumulation in host gastric cells, triggers cancerous progression. The obtained results are quite interesting and provide hidden molecular level information regarding the activity of *H. pylori* that it can probably switch the system to cancerous state. Moreover, the impact of the *H. pylori* on p53 regulatory pathway should be further studied in realistic system in order to capture the state switching mechanism quantitatively and to understand the role of noise in the cellular process.

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